HEALTH EFFECTS DOCUMENT

ON NICKEL

Submitted to

Ontario Ministry of Labour

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The opinions, findings and conclusions contained herein are those of the authors and do not necessarily constitute endorsement by the Ontario Ministry of Labour

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FOREWORD

At the request of the Ontario Ministry of Labour, the Department of Environmental Medicine at Odense University submitted a proposal for cooperation on development of a Health Criteria Document for Inorganic Nickel. This proposal was selected for funding by the Ministry. The present report is the outcome of this cooperative effort.

During the 10-month project, an inspiring cooperation has been enjoyed. In particular, the project officer of the Ministry, Dr. Jean O'Heany has carefully followed every development and supported the work in all aspects. Several meetings have taken place in Toronto, and Dr. G.R.Wright and Dr. J.R.Stopps have commented on various drafts and suggested improvements. Excursions were also arranged to two major nickel-producing facilities in Sudbury, Ontario. The final editorial changes were made during Dr. O'Heany's visit to Odense, Denmark, in April, 1986.

At Odense University, Dr. Gitte Dalsgaard Nielsen and Dr. Ole Andersen have been the driving forces throughout the project. In addition, Dr. Allan Astrup Jensen of the Danish National Institute of Occupational Health wrote drafts on chemical aspects and reviewed the report with regard to chemistry. More than 1000 references were skillfully entered into a computerized data file, from which the reference list was extracted; Caroline Olson was in charge of these operations. The secretarial staff included Inge Bøgelund, Yrsa Kildeberg and Gitte Tajouri who handled complicated manuscripts with great expertise despite numerous changes.

The development of this document was greatly aided by the continuous support by Dr. F.William Sunderman, Jr., Professor of Laboratory Medicine and Pharmacology at Connecticut University School of Medicine. Dr. Sunderman also reviewed one of the final drafts and made useful comments which considerably improved the quality of the report.

Odense University, May 1986 Ph.Grandjean

GLOSSARY

AAS	Atomic absorption spectrophotometry.
Accuracy	The degree to which a measurement, or an estimate based on measurements, represents the true value of the attribute being measured.
ACGIH	American Conference of Governmental Industrial Hygienists.
Adenoma	A benign epithelial tumour
Allergy	A hypersensitive state acquired through exposure to a particular allergen, reexposure bringing to light an altered capacity to react, e.g., allergic contact eczema.
Alloy	A mixture of two or more elements, at least one being a metal. The properties of alloys are often greatly different from those of the individual components.
Alveoli	Air sacs of the lungs.
Asthma	A condition marked by recurrent attacks of paroxysmal dysphoea, with wheezing due to spasmodic contraction of the bronchi. In some cases, it is an allergic manifestation in sensitized persons.
Bias	Any effect at any stage of investigation or inference tending to produce results that depart systematically from the true values.
Bias, detection	Due to systematic error(s) in methods of ascertainment, diagnosis, or verification of cases in an epidemiologic survey, study or investigation.
Bias, information	A flaw in measuring exposure or outcome that results in differential

	quality of information between compared groups.
Bias, lead-time	A systematic error arising when follow-up of two groups does not begin at strictly comparable times. Occurs especially when one group has been diagnosed earlier in the natural history of the disease than the other group.
Bias, selection	Error due to systematic differences in characteristics between those who are selected for study and those who are not.
Calcination	Heating of a solid to a temperature below its melting point to bring about a state of thermal decomposition. Thereby, sulfur is driven off from nickel sulfide but agglomeration of fine particles does not occur.
Carcinogen	A substance or agent initiating or promoting the development of cancer.
Carcinoma	A malignant growth of epithelial cells tending to infiltrate surrounding tissue and to give rise to metastases.
Carcinoma <u>in situ</u>	A neoplastic entity wherein the tumour cells have not (yet) invaded the adjacent tissue but are still confined to the epithelium of origin.
Case-control study	A study that starts with the identification of persons with the disease of interest, and a suitable control group of persons without the disease. The relationship of an attribute to the disease is examined by comparing the diseased and non-diseased with regard to how frequently the attribute is present or if quantitative, the levels of the attribute in each group.

Chelate	Coordination compound in which a central metal ion is attached by coordination links to two or more nonmetal atoms in the compound. This property is often used in therapy and analytical chemistry.
CHO	Chinese hamster ovary, cells used for *in vitro* studies.
Clastogenic	Causing chromosomal damage.
Cohort	Any designated group of persons who are followed or traced over a period of time.
Cohort study	The method of epidemiologic study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed, or exposed in different degrees, to a factor or factors hypothesized to influence the probability of occurrence of a given disease or other outcome.
Confounding variable	A factor that distorts the apparent magnitude of the effect of a study factor on risk. Such a factor is a determinant of the outcome of interest and is unequally distributed among the exposed and the unexposed.
Contact dermatitis	Acute dermatitis (eczema) due to contact with a corrosive/irritant substance or a substance to which the person is allergic.
Converting	Removal of iron by oxidation and concentration in slag; also includes control of amount of sulfur in subsequent operation with excess driven off as SO_2.
Cross-sectional study	A study that examines the relationship between diseases and other

	variables of interest as they exist in a defined population at one particular time.
Cytosol	The liquid medium of the cytoplasm (the protoplasm of the cell exclusive of the nucleus).
Cytotoxicity	Deleterious effects upon cells.
d	Day(s)
Dermatitis	Inflammation of the skin.
Dysplasia	Abnormality of size, shape and organization of cells, often seen as an early stage in the development of cancer.
Electrolysis	Chemical changes produced by passage of an electric current through an electrolyte.
Electrolyte	A substance that, when dissolved in a solution, becomes an ionic conductor.
Electroplate	To plate with an adherent continuous coating by electrodeposition.
Endocytosis	The uptake by a cell of particles and droplets too large to diffuse through the cell membrane. Includes both phagocytosis of particles and pinocytosis of extracellular fluid.
Epithelium	The membranous cellular tissue that constitutes the outer layers of the skin or lines the body cavities.
Erythrocytosis	An increase in the total amount of red blood cells.
Erythropoiesis	The formation of red blood cells.
Genotoxic	Causing damage to the genetic material.

h	Hour(s)
Half-life	The time it takes untill half of the original concentration or amount is left (also called half-time and abbreviated $t_{1/2}$).
Incidence	The number of instances of illness commencing, or of persons falling ill, during a given period in a specified population.
Incidence rate	A measure of the rate at which new events occur in the population.
Inference	The act of passing from observations to generalizations.
Intraocular	Into the eye.
Intrarenal	Into the kidney.
Intravenous (i.v.)	Into a vein.
Intramuscular	Into a muscle.
Intraperitoneal (i.p.)	Into the cavity of the abdomen lined by the peritoneal membrane.
Latent period	Delay between exposure to a disease-causing agent and the appearance of manifestations of the disease.
Leukocytosis	An increase in the number of white blood cells.
Matching	The process of making a study group and a comparison group comparable with respect to extraneous factors.
Matte	A crude mixture formed in smelting sulfide ores.
Metaplasia	A change in the type of tissue cells to a form abnormal for that tissue, e.g., the change of cylindrical, respiratory epithelium to squamous

	epithelium. Often regarded as a sign of potential cancer development.
min	Minute(s)
Misclassification	The erroneous classification of an individual, a value or an attribute into a category other than that to which it should be assigned.
MMAD	Mass median aerodynamic diameter (of a particle).
Mutagen	A substance that causes an increase of the frequency or extent of mutation.
Neoplasia	Formation of tumours.
NIOSH	National Institute for Occupational Safety and Health.
OSHA	Occupational Safety and Health Administration (US Department of Labor).
P-value	The letter p (probability) followed by the abbreviation n.s. (not significant; or by the symbol < (less than) and a decimal notation such as 0.01, 0.05, is a statement of the probability that the difference observed could have occurred by chance, if the groups compared are really alike.
Phagocytosis	The engulfing of foreign particles or microorganisms by cells.
Pneumoconiosis	Fibrosis of the lungs caused by the inhalation of irritant mineral or metallic particles.
Prevalence	The number of instances of a given disease or other condition in a given population at a designated time.
Prevalence rate	The total number of all individuals

	who have an attribute or disease at a particular time divided by the population at risk of having the attribute or disease at this point in time or midway through the period.
Random	Governed by chance; not completely determined by other factors.
Reduction (of nickel)	Conversion of nickel oxide to nickel metal.
Reliability	The degree of stability exhibited when a measurement is repeated under identical conditions.
Retrospective study	A research design which is used to test etiologic hypotheses in which inferences about exposure to the putative causal factor(s) are derived from data relating to characteristics of the persons under study or to events or experiences in their past.
Reverberatory	Type of furnace in which heat is radiated from the roof onto the material treated.
Risk	A probability that an event will occur, e.g., that an individual will become ill or die within a stated period of time or age.
s	Second(s)
Sarcoma	A malignant tumour of mesenchymal (connective tissue) origin.
SCE	Sister chromatid exchange.
Screening	The presumptive identification of unrecognized disease or defect by the application of tests, examinations or other procedures which can be applied rapidly.
Sensitivity	Sensitivity is the proportion of

	truly diseased persons in the screened population who are identified as diseased by the screening test.
SHE	Syrian hamster embryo, cells used for *in vitro* studies.
Sintering (of nickel)	Heating and oxidizing nickel sulfide to nickel oxide whereby sulfur is driven off feed material and agglomeration of fine particles occurs.
Smelting (of nickel)	Thermal treatment of nickel sulfide ores or ore concentrates to bring about physical and chemical changes leading to recovery of nickel and valuable metals.
Specificity	The proportion of truly nondiseased persons who are so identified by the screening test.
Spectrophotometry	Use of a photometer for measuring relative intensities of light in different parts of a spectrum.
Standardized mortality ratio (SMR)	The ratio of the number of deaths observed in the study population to the number of deaths expected if it had the same rate structure as the standard population.
Statistical significance	Statistical methods allow an estimate to be made of the probability of the observed or greater degree of association between independent and dependent variables under the null hypothesis. From this estimate, in a sample of given size, the statistical "significance" of a result can be stated. Usually the level of statistical significance is stated by the P-value.
STEL	Short-term exposure limit, i.e., the maximum concentration allowed where

	workers can be exposed to a substance for a period up to 15 minutes continuously.
Subcutaneous (s.c.)	Under the skin.
Synergism	A situation in which the combined effect of two or more factors is greater than the sum of their solitary effects. When two factors act synergistically persons will get the disease when exposed to both factors but not when exposed to either alone.
Teratogen	A substance tending to cause developmental malformations of the foetus.
TLV	Threshold limit value.
TWA	Time-weighted average concentration of a substance in the workplace, usually measured on the basis of an 8-h work-day or over a 40-h workweek.
Validity	This term has several meanings, usually accompanied by a qualifying word or phrase.
Validity, measurement	An expression of the degree to which a measurement measures what in purports to measure.
Validity, study	The degree to which the inference drawn from a study, especially generalizations extending beyond the study sample, are warranted when account is taken of the study methods, the representativeness of the study sample and the nature of the population from which it is drawn.

EXECUTIVE SUMMARY

Nickel is a transition group metal with many useful properties and a wide range of applications in alloys and a large number of compounds. The world's largest deposit of nickel sulfide ore is located in the Sudbury, Ontario, area where it has been mined, smelted and refined since the beginning of this century. About 16,000 employees are exposed to nickel at the production facilities in Ontario, and at least 9,000 workers are exposed to airborne nickel in the nickel-using industries. In addition, nickel exposures may occur irregularly in several occupations where nickel compounds are used, and dermal exposures are likely to occur rather widely. Current exposure levels are rarely above 0.2 mg/m^3, although certain operations may entail exposures up to 1 mg/m^3. Additional nickel exposures originate from food and drinking-water, including nickel leached from containers and utensils. Past occupational exposures to nickel were much in excess of current levels, but are difficult to evaluate in detail. This problem is of significance, as the delayed health effects seen now are a result of exposures a long time ago. Current methods for monitoring of airborne nickel could be used to assess compliance with exposure limits of about 0.01 mg/m^3 and above.

Nickel in the body exists as sparingly soluble compounds retained in the lungs and lymph nodes, and as systemically distributed coordination complexes of absorbed nickel. The pulmonary deposition, retention, clearance and absorption are governed by the physico-chemical properties of the particles and aerosols. Dermal absorption is limited but is of significance for nickel-allergic patients. Gastrointestinal absorption of soluble nickel compounds is usually about 2-5%, but may be more when the stomach is empty. In the blood, nickel is mainly located in the serum after absorption, and most of the nickel is bound to albumin. Relatively much nickel is transferred rapidly to the kidneys, from which it is subsequently excreted. Lesser amounts are transferred to the lungs and the skin where, on the other hand, the retention time is longer.

Tissue and body fluid concentrations of nickel are elevated considerably after pulmonary exposure to soluble compounds, while undetectable or only slight elevations result from exposure to sparingly soluble nickel compounds. Such compounds may be taken up especially by phagocytes in particular crystalline nickel compounds with a negative surface charge, such as nickel subsulfide. The genotoxic activity of the nickel compounds may be related to the rate of cellular uptake. Also, compounds sparingly

soluble in water may be more rapidly solubilized in cytosol and serum, and the intracellular distribution of nickel may be different from that resulting from uptake of soluble nickel compounds. The genotoxic potential is likely to be related to these properties.

Genotoxic effects of nickel ions *in vitro* have been demonstrated by several means. Studies have shown effects on the genetic material in cell-free systems and mutagenicity in some microorganisms, but not in others, as well as in cultured mammalian cells. Chromosomal damage, sister chromatid exchange and cellular transformation have also been documented, some of these effects even in cultured human cells. Although dose-response relationships have been obtained in several studies, these are difficult to translate to human exposure situations. The effects have been caused by sparingly as well as by easily soluble nickel compounds, and the magnitude of the effects may be related by the degree of cellular toxicity and perhaps the intracellular nickel concentration. Sparingly soluble, crystalline compounds may exert particularly intensive effects in phagocytic cells due to their rapid uptake. Thus, although the nickel ion may be the ultimate carcinogen, the concentration at the cellular target is difficult to predict when complicated by different uptake and solubilization kinetics.

Nickel compounds, in particular alpha-nickel subsulfide have been used as model compounds in carcinogenesis research. The scientific studies in this area have resulted in a large number of papers of major interest. Unfortunately, the studies deal primarily with mechanisms of carcinogenesis and development of animal models, rather than prediction of cancer in relation to occupational and environmental exposures. Thus, the evidence dealing with pulmonary and oral exposure to nickel is limited and does not satisfy the requirements for carcinogenesis assays. However, a series of studies using intramuscular and intrarenal injection suggests that several nickel compounds are carcinogenic and that the potential varies for different compounds. Further, intrarenal injection of several nickel compounds results in two events which appear to be related: development of carcinoma and stimulated erythropoiesis, perhaps both being a result of cellular dedifferentiation or neoplastic transformation. Although the kinetics of nickel in the body and within the cells are not understood to a sufficient degree, this evidence again points to the nickel ion as the ultimate carcinogen. However, the evidence available does not allow any firm conclusions to be drawn concerning human exposure settings.

The carcinogenic effects of nickel occur with a considerable latency time after the initiation of exposure. Thus, the health effects found in epidemiological studies now are the result of exposures decades ago. This is a problem of major significance, as the magnitude and exact speciation of past exposures is difficult to evaluate. Several studies have been carried out at nickel smelters and refineries. Although each of them suffers from some deficiencies, as are normal in such retrospective studies, the findings in concert strongly indicate that nickel from the calcining and sintering operations is a potent carcinogen resulting in nasal and pulmonary cancers. Some risk appears to be present in other operations, such as Orford furnace, copper sulfate and crushing departments, and one study has suggested a risk associated with soluble nickel compounds in the electrolysis department, although this finding has not been confirmed. Only one study demonstrated an exposure-response relationship which, however, was not statistically significant. In other studies, a relationship between increased exposure time and cancer risk could be demonstrated. In nickel-using industries, no excess cancer related to nickel exposures has been demonstrated beyond doubt; in many cases, concurrent exposures to other potential carcinogens constitute a confounding variable which makes it difficult to interpret the findings. However, the studies have not excluded that the cancer hazard is restricted to the nickel-producing facilities only. Further, case-referent studies of respiratory cancers suggest that a nickel-related etiology may well exist in the nickel-using industries.

Nickel may have profound effects on the immune system. First of all, nickel is a common skin allergen, in recent studies the most frequent cause of allergic contact dermatitis in women and one of the most common causes in men. The sensitization appears to occur mainly in the young age groups, usually caused by non-occupational skin exposures. However, subsequent provocation of hand eczema may be caused by occupational exposures, especially to nickel-containing fluids and solutions. In some cases, the hand eczema may cause incapacitation. In addition, several cases of nickel-associated asthma have been described, and this disease may not be as rare as indicated by the few case reports. Further, nickel has been shown in experimental studies to cause immunotoxic effects, in particular increased infectiousness, decreased natural killer cell activity, inhibition of interferon production and interference with functions of the complement system. Although some of these effects have been demonstrated at concentrations likely to occur under occupational exposure conditions, the health significance of these findings is difficult to evaluate. However, immunotoxic effects could contribute to the

development of cancer.

A range of reproductive effects may be induced by nickel in experimental animal studies. However, the doses used are rather high and may not relate at all to human exposures. Further, the mechanism of the effects seen is unclear. No information on reproductive effects in humans caused by nickel has been found. Thus, at this point, reproductive effects do not seem likely to occur in humans as a result of occupational exposures if other toxic effects are prevented.

Nickel is an essential nutrient in several species and may, in minute amounts, have essential biochemical functions in humans. The health-related concern in regard to human nickel exposures is due to toxic effects of increased intake. Acute manifestations include symptoms and signs from the central nervous system, kidneys, heart and lungs. Only one death due to acute nickel intoxication has been recorded. Kidney toxicity mainly relates to tubular dysfunction with increased levels of small-molecular-size proteins and amino acids in the urine, as documented in experimental studies and in nickel electrolysis workers. Pulmonary effects have not been studied in detail in humans, but experimental animal data strongly indicate considerable effects of 0.1 and 0.2 mg Ni/m^3 on surfactant production, type II cells and macrophages. Nickel interferes with heart muscle and smooth muscle contraction and causes a significant increase of coronary vessel resistance even at a nickel level of 6 ug/l in the perfusion fluid.

In the absence of detailed dose-response relationships and definite thresholds, exposure levels for nickel and inorganic nickel compounds should be kept as low as reasonably achievable. An exposure level no higher than 0.1 mg/m^3 is likely to protect against most adverse effects, although a lower level would be indicated for the nickel-producing industry. Skin contact should be limited, and dermal exposure to soluble nickel compounds should be prevented. As some effects are related to circulating, dissolved nickel in the body, biological monitoring of serum/-plasma nickel levels should be offered as part of a health surveillance programme. Nickel levels should be kept below 5 ug/l serum or plasma. Neither chest X-ray nor sputum cytology can be considered obligatory items, but nasal biopsy or exfoliative cytology would be useful for employees with high exposures in the past. The health surveillance should emphasize early detection of possible effects on lungs, heart, kidneys and skin.

1. INORGANIC NICKEL IN OCCUPATIONAL EXPOSURES

1.1 The element

Nickel is the 28th element and was discovered by the Swedish chemist A. F. Cronstedt in the mid-1700s. In the periodic table of elements, nickel is placed in the first transition series group VIII together with iron and cobalt. It occurs as a mixture of 5 natural isotopes. Some physical constants are given in Table 1. This section and sections 1.2 and 1.3 are based on several chemical handbooks and reviews (Hampel, 1973; Bennett, 1974; IARC, 1976; Windholz, 1976; Cotton and Wilkinson, 1980; Weast, 1980-1981; Clayton, 1981; Kirk-Othmer, 1981; Sax, 1984; Neumuller, 1985).

Nickel is a silver-white metal with typical metal properties. It exists in two crystalline modifications: alpha-nickel with a hexagonal lattice and beta-nickel with a cubic lattice. Alpha-beta transition occurs when heated to more than 250°C. Nickel has high electrical and thermal conductivities (both about 15% of those of silver), and can be drawn, rolled, forged and polished. It has a high melting point and is ferromagnetic at temperatures below 360°C but not as much as iron.

Nickel is quite resistant to corrosion by air, water or alkaline solution at ordinary temperatures and is therefore often used for electroplating to produce a protective coating. However, finely divided nickel is reactive in atmospheric air and may be pyrophoric under some conditions.

Nickel is moderately electropositive and dissolves readily in dilute mineral acid to form green nickel(II) salts. Nickel is insoluble in concentrated nitric acid which renders it passive (oxide film) but powdered nickel may be dissolved in warm nitric acid.

1.2 Nickel alloys

Nickel is one of the important alloying elements for steel and cast iron. Used with other alloying elements, such as chromium and molybdenum, it gives strength, toughness and wear resistance that are essential for automotive parts, heavy machinery, transportation and construction applications. Nickel is an ingredient of the popular 18% chromium-8% nickel stainless steels, particulary noted for their corrosion resistance, good formability, weldability and desirable mechanical properties at both low and elevated temperatures. These alloys are widely used in the

chemical, transportation and petroleum industries; for food processing and handling, dairy and pharmaceutical equipment; in hospitals and for domestic houseware applications, as well as building materials. More than 3000 nickel alloys are used in industrial applications, e.g., nickel-copper alloys for coins, nickel-aluminium alloys for aircrafts or nickel-copper-zinc alloys for jewelry. Some important alloys and their melting points are listed in Table 2.

1.3 Nickel Compounds

This document deals with inorganic nickel only. Nickel carbonyl is considered an organic nickel compound due to the covalent character of the nickel-carbon bond, and all organonickel compounds have not been dealt with.

Nickel forms a very extensive series of inorganic compounds. Normally, only nickel (II) compounds are stable, but oxidation level (III) and (IV) may occur, e.g., in oxides. Tables 3 lists some of the most important nickel compounds and their physical and chemical properties with examples of current or potential uses.

Solubility is a property of special importance in the toxicology of nickel. In general, nickel salts of strong acids and organic acids are quite soluble in water. Nickel salts of weak inorganic acids are insoluble in water but often readily soluble in mineral acids or aqueous ammonia (formation of blue tetrammine complexes). The more insoluble sulfides and selenides are soluble in hot nitric acid or aqua regia. In aqueous solutions, nickel occurs mostly as the green hexaquonickel(II) ion, $Ni(H_2O)_6^{2+}$.

Some of the more important nickel compounds are discussed in further detail below. Some of these compounds, especially oxides, sulfides, selenides, tellurides and arsenides form phases of variable composition with metal defects; such nonstoichiometric compounds are in many respects similar to alloy phases.

1.3.1 Nickel oxides

Nickel(II) oxide (NiO) exists in various crystalline forms. A green cubic form can be formed by firing wet nickel powder in air or by thermally decomposing (1000°C) nickel hydroxide, carbonate, oxalate or nitrate; it is an inert and refractory material with a high melting point. This form is insoluble in water but soluble in acids, unless a grey-black octahedral form has been created at high temperature. A black microcrystalline form results from cal-

cination of the carbonate or nitrate; it is more reactive chemically and more soluble and contains slightly more oxygen than the green stoichiometric form. Thus, the solubility of NiO in acids depends on the specific method of manufacture and heat treatment.

Partly reduced nickel oxide products, known as "nickel oxide sinters", are produced commercially on a large scale by roasting and converting refined nickel ores. The green and black nickel oxides are used in nickel refining and manufacture of glass (grey colour), ceramics and nickel catalysts. Black nickel oxide is used for the production of nickel salts.

Both Ni(III) and Ni(IV) oxides are known, but neither type has been obtained in a pure state. Nickel(III) oxide (Ni_2O_3 or $NiO(OH)_2$) forms a black solid when a suspension of nickel(II) hydroxide in potassium hydroxide solution is treated with a fairly mild oxidizing agent such as bromine. A dihydrate may be isolated after vacuum drying. This compound is insoluble in water but soluble in hot mineral acids. With a stronger oxidizing agent, such as chlorine, a dark precipitate of impure, possibly hydrated, nickel(IV) oxide ($NiO_2 \cdot nH_2O$ is formed. Both these oxides are very unstable and are very strong oxidizing agents in the presence of acids. They may even convert Mn(II) to permanganate. Nickel(III) oxide is one of the electrodes in the Edison, or nickel-iron, battery.

1.3.2 Nickel(II) hydroxide

This compound ($Ni(OH)_2$) may, on addition of alkali metal hydroxides, be precipitated from aqueous solutions of Ni(II) salts as a voluminous green gel which, with time, becomes crystalline. Nickel hydroxide is insoluble in water but readily soluble in acids and in aqueous ammonia owing to the formation of blue tetrammine complexes. It is also soluble in alcohol. Nickel hydroxide is an intermediate in the manufacture of nickel catalysts, but the major use is in the manufacture of nickel-cadmium batteries.

1.3.3 Nickel(II) sulfates

Both an anhydrous compound ($NiSO_4$) and hexa- and heptahydrates occur. The sulfate can be made by adding nickel powder or black nickel oxide to hot, dilute sulfuric acid or by reacting nickel carbonate with (cold) dilute sulfuric acid. When the solution is concentrated, the heptahydrate ("nickel vitriol") precipitates as green rhombic crystals which convert to the hexahydrate when heated to 31.5°C. The hexahydrate forms blue or blue-green tetra-

gonal crystals (alpha form) which change to the green monoclinic beta form at about 53°C. This compound loses 5 water molecules at about 100°C, and a greenish-yellow anhydrous sulfate is formed by heating to 280°C. Heating to decomposition at about 800°C will release fumes of sulfur dioxide.

The sulfates are soluble in water and alcohols, although anhydrous nickel sulfate dissolves only slowly in cold water. Nickel sulfate, hexahydrate, is mainly used as an electrolyte in nickel plating or nickel electrorefining. It is also used as an intermediate in the manufacturing of other nickel compounds and catalysts, as a mordant in dyeing and printing fabrics, and in blackening zinc and brass.

Nickel sulfate forms a number of double salts, e.g., ammonium nickel sulfate is prepared by reacting nickel sulfate with ammonium sulfate. It is a major salt used in electroplating in Ontario and elsewhere.

Another double salt with cobalt is used in dyeing, printing, etc.

1.3.4 Nickel(II) nitrate

Nickel nitrate ($Ni(NO_3)_2$) may by prepared by the reaction of dilute nitric acid and a nickel carbonate. A hexahydrate crystallizes from saturated aqueous solutions as green, monoclinic, deliquescent crystals which are very soluble in water and soluble in ethylene glycol and hydrazine. It is a strongly oxidizing agent and a dangerous fire risk. The hexahydrate loses water by heating, but anhydrous nickel nitrate, which is unstable, decomposes to nickel oxide.

Nickel nitrate is an intermediate in the manufacture of nickel catalysts and Ni-Cd batteries. Furthermore, it is used in nickel plating and in ceramics (brown colour). Reduction of nickel with hydrogen yields nickel metal powder with a large surface area, thus making it useful as a catalyst.

1.3.5 Nickel(II) carbonates

Pure nickel carbonate ($NiCO_3$) is a light-green, rhombic crystalline salt which is insoluble in water but soluble in hot hydrochloric acid and aqueous ammonia. It is usually prepared by the oxidation of nickel powder in ammonia and carbon dioxide, followed by removal of the ammonia by boiling.

The addition of sodium carbonate to a solution of a nickel salt

precipitates an impure carbonate hydroxide, mainly pentanickel dicarbonate hexahydroxide or tetrahydrate, which is an important commercial product. It is used in the production of nickel catalysts. A high-purity compound is used in electronic components. Furthermore, it is used as a pH regulator in plating.

1.3.6 Nickel(II) fluoride

Anhydrous, brownish-green nickel difluoride (NiF_2) with rutile lattice structure may be prepared by heating the double salt, diammonium nickel tetrafluoride. It may also be prepared from fluorine and nickel powder. This salt is slightly soluble in water but easily soluble in acids, alkalis and ammonia. A pale-green tetrahydrate is stable and more water soluble. This compound is used in batteries.

1.3.7 Nickel(II) chloride

Anhydrous, yellow nickel dichloride ($NiCl_2$) may be prepared by direct reaction of the elements or chlorination of nickel oxide. It is paramagnetic and soluble in water, ethanol, ethylene glycol and hydrazine. The green hexahydrate may be formed by the reaction of nickel powder or nickel oxide with hot hydrochloric acid. This compound is a principal nickel compound used in electroplating in Ontario and elsewhere. Nickel dichloride is an intermediate in the manufacture of nickel catalysts and is used in gas masks to absorb ammonia.

1.3.8 Nickel(II) bromide

Anhydrous, orange nickel dibromide ($NiBr_2$) is prepared from the elements. It is very soluble in water. The hexahydrate is made from black nickel oxide and hydrogen bromide. It has limited use in electroplating, but is used as a catalyst for polymerization and other chemical reactions.

1.3.9 Nickel(II) cyanide

A grey-blue, tetrahydrated form ($Ni(CN)_2 \cdot 4H_2O$) is precipitated by addition of cyanide ions to aqueous nickel(II) solutions. The precipitate dissolves in excess cyanide to form the yellow tetracyanoniccolate ion ($Ni(CN)_4^{2-}$). In general it is soluble in bases. A yellow-brown anhydrous compound ($Ni(CN)_2$) is formed by heating the hydrate to 180-200°C. Nickel cyanide is used as a catalyst for acetylene reactions. Potassium tetracyanoniccolate is used as an additive in plating with gold and silver.

1.3.10 Nickel sulfides

Nickel monosulfide (NiS) exists in polymorphous forms. Addition of sulfide ions to aqueous solutions of nickel (II) ions precipitates black amorphous alpha-NiS. Initially, it is soluble in hydrochloric acid, but on exposure to air it soon becomes insoluble by conversion to polysulfides or hydroxysulfide (Ni(OH)S). As most nickel sulfides it is soluble in hot nitric acid or aqua regia. Heating of the elements in a vacuum-tube at about 900°C forms beta-NiS as hexagonal crystals (NiAs lattice). This modification may be deficient in nickel ($Ni_{1-x}S$). At temperatures <400°C gamma-NiS formed as a rhombohedral modification (tetragonal pyramid), stable at normal temperatures and occurring in nature as the mineral millerite (which has been named beta-NiS, e.g., by Sunderman (1984)). The solubility of the sulfides in water and acids decreases from alpha-NiS through beta-NiS to gamma-NiS. NiS has importance in manufacturing catalysts.

Nickel disulfide (NiS_2) occurs as the dark-grey mineral vaesite. It is formed by heating (400°C) a stoichiometric mixture of the elements. It decomposes into beta-NiS and sulfur.

Trinickel tetrasulfide (Ni_3S_4) occurs as the black-grey mineral polydomite. It may be formed from a mixture of gamma-NiS and nickel disulfide at 200°C.

Trinickel disulfide (nickel subsulfide, Ni_3S_2) exists in a bronze-yellow high temperature modification (beta-Ni_3S_2). It may be formed by heating the elements in quartz tubes at >600°C. At lower temperatures it transforms to a green beta-form which is stable at normal temperature, and may be formed electrolytically. The grey mineral heazlewoodite is the same modification, but has been named alfa-nickel subsulfide. Nickel subsulfide may be formed during the production of nickel from sulfide ores. Although insoluble in water and most acids, it may be dissolved in biological fluids, such as serum (as discussed in section 2.9).

1.3.11 Nickel selenides

Three modifications of nickel monoselenide (NiSe) may be precipitated by selenide ions from aqueous solutions of nickel. In basic to neutral solution, amorphous and unstable alpha-NiSe is formed. In acetic acid hexagonal beta-NiSe with NiAs lattice is formed, and in mineral acid rhombic gamma-NiSe is formed. Nickel selenide, which occurs as the grey mineral maekinerite, is slowly oxidized to selenite. Therefore, it is soluble in bromine water and, slowly, in nitric acid.

Nickel diselenide has a certain region of homogenicity between $NiSe_{1.95}$ and $NiSe_{2.05}$. It has a pyrite structure.

Nickel subselenide (trinickel diselenide, Ni_3Se_2) exists in a high-temperature modification of unknown structure (beta-Ni_3Se_2) At temperatures <600°C, the stable modification is alpha-Ni_3Se_2 with the same structure as haezlewoodite.

1.3.12 Nickel tellurides

Nickel monotelluride (NiTe) is formed as red-grey hexagonal crystals (NiAs latice) by heating the elements (powder) in a quartz tube at 800°C, but it may not exist as such. It is a mixture of $NiTe_{0.9}$ and $NiTe_{>1-2}$. It is easily oxidizable and soluble in bromine water.

1.3.13 Nickel arsenides

Nickel monoarsenide (NiAs) occurs as the grey mineral niccolite with a hexagonal crystal structure. At heating to 800°C, NiAs degrades to grey tetragonal crystals of undecanickel octaarsenide ($Ni_{11}As_8$) which is soluble in nitric acid and aqua regia. It occurs as the mineral maucherite. Pentanickel diarsenide (Ni_5As_2) is formed by heating the elements to 1000°C. Nickel arsenic sulfide (NiAsS) occurs as the mineral gersdorffite. It is a mixture of $Ni_{1\pm x}As$ and $Ni_{1-x}S$.

1.3.14 Nickel(II) arsenate

Trinickel diarsenate octahydrate ($Ni_3(AsO_4)_2 \cdot 8H_2O$) is a yellowish-green powder which is insoluble in water but soluble in acids. It is prepared from arsenic acid and nickel carbonate and occurs naturally as the mineral annabergite. It may be used as a catalyst for hydrogenation of fats.

1.3.15 Nickel(II) phosphate

Nickel forms a large numner of phosphates of various types. Trinickel diphosphate heptahydrate ($Ni_3(PO_4)_2 \cdot 7H_2O$) or octahydrate exists as green plates, insoluble in water but soluble in acids. It is prepared from nickel carbonate and hot dilute phosphoric acid. It is used for steel coating and pigment production.

1.3.16 Nickel(II) acetate

This salt ($(CH_3COO)_2Ni$) may be produced by reacting nickel oxide or carbonate with acetic acid or from sodium acetate and nickel sulfate in solution. It is very soluble in water. A green crystalline tetrahydrate may be isolated. This salt is used mainly as a mordant in the textile industry and, to a minor extent, as a hydrogenation catalyst.

1.3.17 Nickel(II) formate

The dihydrate of this salt ($(HCOO)_2Ni \cdot 2H_2O$) is prepared as green crystals from nickel or nickel carbonate and formic acid. It is soluble in water but not in alcohols and is used in the preparation of nickel hydrogenation catalysts.

1.3.18 Nickel(II) sulfamate

This salt ($Ni(NH_2SO_3)_2 \cdot 4H_2O$) is produced by reaction of nickel powder or black nickel oxide with a hot-water solution of sulfamic acid. It is easily soluble in water and is used as an electrolyte in nickel electroforming systems.

1.3.19 Nickeltetrafluoroborate

This complex ($Ni(BF_4)_2$) may be formed as apple-green hexahydrate needles from nickel carbonate by reaction with fluoroboric acid. It is very soluble in water and soluble in ethanol and ethanol/ether mixtures and is used as an electrolyte in high-speed nickel plating.

1.3.20 Nickel oxalate

This compound ($(COO)_2Ni$) is formed as a green crystalline dihydrate from nickel solutions and alkali oxalate. It is insoluble in water but dissolves in acids with decomposition and in ammonia with the formation of an ammine. This salt is used for production of very pure nickel oxide or finely divided nickel for catalytic purposes.

1.4 Nickel ores and nickel production

The discovery of nickel ore deposits, the development of nickel mining technology and the growth of the operations are described in detail by Thompson and Beasley (1960), Boldt and Queneau (1967) and Warner (1984). The following brief account is based on these reviews and other sources as indicated.

1.4.1 Nickel ores

Several minerals contain nickel (Table 4). About 55% of the nickel produced in the western world is extracted from sulfide ores. The largest deposit known is located in the Sudbury, Ontario, area. The major sulfide ore is pentlandite, $(Ni,Fe)_9S_8$, which is associated with nickeliferous pyrrhotite, $(Fe,Ni)_{1-x}S$. Other, less-common minerals of the Fe-Ni-S system occur as well. While pentlandite may contain about 35% of nickel by weight, the nickel content of the pyrrhotite is much less, and the sulfide ore available for nickel production generally holds only 1-2% nickel.

About 80% of known nickel deposits are in the form of oxide ores, and they now contribute only 45% of nickel production in the western world. These ores developed under tropical climate conditions, where laterization resulted in dissolution, removal and redeposition of minerals, which under certain conditions created nickel/ferrous laterites with nickel contents up to 2.5%. The chemical form of the nickel-bearing minerals varies and is extremely complex. Thus, the nickel deposit in Douglas County, Oregon, USA, is mainly in the form of silicates, such as garnierite, a magnesium silicate, with iron oxides, magnesia and silica making up the major constituents of the ore; the average nickel content is just above 1%. Also, the large open-pit mines in New Caledonia produce only oxidized nickel ore.

1.4.2 Nickel production from sulfide ores

The nickel ore is crushed and ground to fine particles in a concentrator plant where grains of other minerals are rejected, thus resulting in a higher nickel content of about 10-15% in the ore concentrate. These operations are generally carried out under wet conditions which cause only low dust levels.

The nickel concentrate may be processed in several ways, though generally in smelters where remaining rock and iron, and much sulfur and copper are removed. The first stage is usually a process called roasting. At temperatures of 650-800°C, nickeliferous pyrrhotite and pentlandite decompose to form mainly nickel-containing iron oxide, nickel subsulfide and smaller amounts of pentlandite and godlevskite (Ni_7S_6). In the past, heap roasting was used for this process. Multiple-hearth roasters have now been substituted in the Ontario smelters. The roasted concentrate is then melted in an electric reverberatory furnace at about 1200°C. The metal sulfides form a matte, on top of which floats an oxide

slag containing the remaining rock and iron oxide. The furnace matte is then transferred to a converter at about 1200°C where atmospheric air is blown through to remove sulfur dioxide and oxidize iron which is skimmed off. The converter (Bessemer) matte is allowed to solidify and consists mainly of nickel subsulfide and copper sulfide.

The converter matte may be refined by several means. In some cases, hydrometallurgical methods are used: after grinding of the matte, and dissolution with an oxidizing agent, the nickel is recovered by electrolysis. Alternatively, if the converter matte has been allowed to cool slowly, nickel subsulfide and copper sulfide crystals may be separated by concentrating techniques. The nickel matte is then roasted to nickel oxide which may be refined electrolytically or by the nickel carbonyl (Mond) process. The latter process includes reduction with hydrogen at 450°C, reaction with carbon monoxide to form nickel carbonyl and subsequent decomposition to pure nickel.

In Ontario, the International Nickel Company, Inc. (INCO) mines and mills nickel ore in the Sudbury area. Some nickel ore concentrate was roasted (at about 600°C) at the Coniston smelter during the period 1914-72; after roasting, ore was heated in a blast furnace. At Port Colborne, the ore concentrate was roasted and oxidized at about 1650°C in open-hearth calciners, and later sintered with coke on travelling grate furnaces; sintering took place from the late 1920s until 1958, calcining from 1921 to 1973 (Chovil et al., 1981). A new sintering plant opened in 1948 at Copper Cliff near Sudbury and continued production until 1963 when the oxidation process was taken over by fluid bed roasters. The matte produced was refined at Port Colborne, from the early 1970s at Copper Cliff, but a considerable part of the matte is exported for refining in Clydach, Wales.

Before 1925, only partially refined ore was shipped to Clydach; it contained impurities of several elements and a large proportion of copper. This material was calcined under very dusty conditions, and copper was removed by leaching with sulfuric acid which may have contained considerable concentrations of arsenic. Subsequently, a refined matte containing much less copper was shipped to Clydach, and improvements in hygiene conditions were also made (Doll et al, 1970).

Matte from Sudbury was also shipped to a nickel refinery at Huntingdon, West Virginia, USA. The calcining process was in operation from 1922 to 1947. Oxidation of the ground matte took place in gas-fired calciners to produce copper-nickel oxide

suitable for manufacture of Monel alloy (Enterline et al., 1982). Falconbridge Nickel Mines, Ltd. operates mines, mills and a smelter at Sudbury. Before 1978, roasting at the smelter was performed at a low temperature, as was the case in the Coniston sinter plant, but this process has now been replaced by multiple-hearth roasters. The matte is shipped to a refinery in Kristiansand, Norway, which began operations in 1910. Roasting, smelting and electrolysis are the main processes here, but considerable changes have occurred over the years, particularly after 1950 (Pedersen et al., 1973).

1.4.3 Nickel production from oxide ores

In general, nickel oxide ores cannot be concentrated by conventional physical processes. Pyrometallurgical methods are usually employed, although hydrometallurgical processes may also be used. Various smelting techniques aim at reducing nickel oxide to a greater extent than iron oxide, thus producing ferronickel or matte with a high nickel content. The smelters in New Caledonia and Oregon, USA, are examples of such processes. Since 1931, the Noumea, New Caledonia, refinery has processed all ore, producing both nickel matte and ferronickel (Lessard et al., 1978). Oxide ore concentrate from Oregon is being refined by hydrometallurgical processes in Fort Saskatchewan, Alberta (Egedahl and Rice, 1984). Several other plants use pyrometallurgical technology.

1.5 Nickel exposures in user industries

Almost half of the nickel produced is used for stainless steel while about 10% is used in alloy steels; cupronickel and other nonferrous, high-nickel alloys account for 20% of the production, electroplating and certain foundry uses for 10%, and a smaller amount for batteries, catalysts, chemicals, etc. (Warner, 1984). Respiratory exposure to nickel occurs in several user industries. A number of occupations with nickel exposures have been identified (Table 5). The review of nickel compounds above (section 1.3) suggests that other occupations could be added.

Occupational cutaneous exposures to nickel may occur in a wide range of jobs (Fisher, 1973; National Academy of Sciences, 1975; Conde-Salazar et al., 1981). In some occupations, the skin may be directly exposed to dissolved nickel, e.g., in the electroplating or electroforming industry (Wall and Calnan, 1980). This exposure may also be relevant, e.g., for hairdressers (Wahlberg, 1975; Marks and Cronin, 1977). Also, janitors are exposed to increasing levels of nickel in water during successive stages of cleaning: a

high level of 90 ug/l was found in water from used cloths, a finding that may be related to frequent dermatitis problems in this occupation (Clemmensen et al., 1981).

1.6 Occupational nickel exposures in Ontario

A survey of occupational nickel exposures in Ontario has been carried out (Acres, 1982), and several important conclusions can be extracted from this report. Almost 150,000 tons of nickel were produced in Ontario in 1980, with only 2 % actually being consumed in this province. Approximately 30-40 % is exported annually as matte for further refining, and additional amounts are exported as alloys and other nickel products. The electroplating industry is the largest user of nickel in Ontario, followed by alloy steel production and foundries. Nickel consumption may increase in the future for purposes such as nuclear generating plants, gas turbine engines, cryogenic containers and pollution abatement equipment, including stack scrubbers.

On the basis of interviews with key executives, the total number of workers exposed to nickel was estimated at about 25,000, almost two-thirds being in the nickel producing industries (Table 6) (Acres, 1982). The number employed in primary nickel production may have decreased since then. However, the extent of occasional exposure in nickel-consuming industries may have been underestimated. Thus a group of miscellaneous sectors, including powder metallurgy and manufacture of nickel salts, special chemicals and welding rods, may employ considerably more than 300 workers with occupational exposure to nickel (Table 6). Also, the extent of cutaneous exposures, e.g., in hair dressers, has not been evaluated in this context.

Levels of airborne nickel have been summarized (Acres, 1982). Nickel levels in the mines are typically about 0.01 mg/m^3, while somewhat higher levels occur in the mills where the wet ore is processed, typically well below 1 mg/m^3. At the smelters, average nickel levels of 0.03-0.05 mg/m^3 occur near roasters, furnaces and converters, but much higher levels have been measured in the matte casting and crushing area. High nickel concentrations may sometimes occur at conveyor belts, during vacuum cleaning and during handling of reverted materials such as flue dusts. In a matte-processing plant, nickel exposures average about 0.2 mg/m^3, although levels are somewhat higher at the matte separation area. In a nickel refinery, the highest averages approach 0.2 mg/m^3 in the feed preparation area and at the converters. Additional exposures occur in iron and copper recovery plants.

Limited evidence suggests that exposures at electroplating operations may be considerable, although an average of only about 1 mg/m^3 was reported (Acres, 1982). Grinding, casting, handling of nickel powder and welding may also cause high nickel exposures.

1.7 Additional environmental nickel exposures

Nickel constitutes about 0.008% of the earth's crust, and nickel ranks as the 24th element in order of abundance (National Academy of Sciences, 1975). Everybody is exposed to nickel, although usually at very low levels. Nickel is a ubiquitous element, and natural levels may be significantly increased by local pollution sources. In general, these exposures are much below occupational exposure levels, but they may be of importance to nickel-allergic patients (section 4.1).

Nickel concentrations in the atmosphere at remote locations are about 1 ng/m^3, a level which would contribute a negligible amount to human absorption of nickel. Soil suspension is believed to be the major natural source of nickel in the atmosphere. Natural sources contribute, on a global scale, about 16% of current nickel levels in the air (Schmidt and Andren, 1980). Burning of residual and fuel oils, nickel mining and refining, and municipal waste incineration result in the majority of anthropogenic nickel emissions to the atmosphere (Schmidt and Andren, 1980). Suburban and rural areas usually exhibit air nickel levels from a few to several ug/m^3, but average levels in cities in excess of 100 ug/m^3 have been documented, and higher community levels have been measured in Sudbury, Ontario (National Academy of Sciences, 1975). With indoor levels somewhat lower than those outside, an exposure level of nickel would generally average about 20 ng/m^3 in urban areas and 10 ng/m^3 in rural areas (Bennett, 1984). Smoking may increase pulmonary intake further due to the nickel content of tobacco (Grandjean, 1984).

The daily oral intake of nickel has been examined by various methods. Thus, total diets have been studied by the duplicate portion method. Of 55 complete 3-5-day diets in Italy, most contained less than 300 ug Ni per day, which was the detection limit, and the average level in the 16 diets with detectable nickel was 350 ug/day (Clemente et al., 1980). A study of hospital diets in the USA showed that the general diet contained 160 ug/day, and special diets varied by less than 40% from this level (Myron et al., 1978). A daily intake of 290 ug was found in a balance study in the USSR (Nodiya, 1972), and another study stated that the daily intake was 0.5 mg without mentioning the method used (Sidorenko and Izkowa, 1975). Faecal nickel excretion

will reflect dietary intakes (except in the case of occupational exposure), because only a small fraction of the nickel in the diet will be absorbed in the gut (section 2.3): an American study showed an average excretion of 260 ug/day (Horak and Sunderman, 1973). Studies of various food items have shown widely varying nickel levels. Thus, Schroeder et al. (1962) found 470 ug in a 1-day hospital diet and estimated the normal daily intake at 300-600 ug, though, with different diets, the nickel intake could vary between 10 and 900 ug per day. A recent study (Nielsen and Flyvholm, 1984) suggested a daily intake of 155 ug in the average Danish diet.

The nickel content of groundwater is usually low. The levels appear to be similar in raw, treated and distributed municipal water (Meranger et al., 1981). The median level in Canada is below 2 ug/l, but high levels occur in Ontario (Meranger et al., 1981). In particular, municipal tap-water near large open-pit mines averaged about 200 ug/l, while a control area showed an average of about 1 ug/l; this difference was also reflected in serum and urine nickel levels (McNeely et al., 1972). Other studies have suggested low background levels in drinking-water, e.g., in Finland an average of about 1 ug/l (Punsar et al., 1975) and in Italy levels mostly below 10 ug/l (Clemente et al., 1980). In the German Democratic Republic, drinking-water from groundwater averaged 10 ug/l, slightly below the amount present in surface water (Schuhmann, 1980). Groundwater pollution with soluble nickel compounds from a nickel-plating facility resulted in nickel levels up to 2.500 ug/l and a median for 12 wells of 180 ug/l (Dominok et al., 1980). Except for such unusual cases, the direct contribution of drinking-water to the daily nickel intake is comparatively small.

Although the addition of nickel to alloys diminishes corrosion, nickel may in fact dissolve under various conditions. The use of kitchen utensils made of pure nickel may be expected to add more than 100 mg of nickel to the daily intake due to leaching processes during food preparation (Boudene, 1979). Less dissolution takes place from alloys with a low nickel content. One hour of boiling in an alloy container having 15% nickel may leach 60 ug of nickel per dm^2 of exposed surface (Boudene, 1979). Several ug of nickel were released from stainless-steel saucepans during up to 1.5 h of boiling, the release being larger at a lower pH (Christensen and Moller, 1978). Accordingly, an increase in nickel concentrations in water has been observed after boiling (Rondia, 1979).

The average contribution from leaching processes to the daily nickel intake is unknown. Cooking ware, kitchen utensils and water piping may occasionally add 1 mg to the daily intake, i.e., much in excess of the intake resulting from nickel in foods and beverages.

1.8 Evaluation of occupational nickel exposures

1.8.1 Assessment of past exposure conditions

Important adverse effects of occupational nickel exposures occur after a considerable latent period. Thus, current cases of nickel-related respiratory cancer are a possible result of exposures which occurred decades ago. In the evaluation of epidemiological results it then becomes important to estimate the degree and speciation of nickel exposures in the past.

In this regard, two problems must be overcome. Current measurements will not apply to past exposure situations because the production processes have been changed and better dust control measures have been installed. Also, past measurements were performed with equipment which would not give the detailed information needed today; most results are from conimetric measurements of the number of airborne particles. The translation of such measurements into units of mass must be done with great caution, preferably aided by simulation experiments. These problems are of prime importance in the evaluation of epidemiological studies, as discussed in section 3.5.1.

Unfortunately, when dealing with an occupational exposure which causes health effects after a long time delay, a paradoxical situation occurs. The preventive efforts of the future must be based on information on health effects seen today as a result of past exposures which may not occur any more.

1.8.2 Concurrent exposures other than nickel

When evaluating the possible health hazards associated with occupational nickel exposures, the confounding effect of concurrent exposures to other materials must be taken into regard. In principle, toxic effects could erroneously be attributed to nickel if such co-existing exposures were not evaluated.

With regard to nickel mining, radon and diesel exhaust exposures are of particular interest in relation to respiratory cancer incidence. The nickel ore in New Caledonia contains small amounts of chrysotile asbestos (Langer et al., 1980). Asbestos is not a

natural constituent of Sudbury nickel ores, although tremolite does occur. However, the Shebandowan ores used by one nickel-producing industry in Ontario contain small amounts of chrysotile asbestos and appreciable amounts of other amphiboles (Acres, 1982). In a Welsh nickel-refining plant, some information suggests that arsenic contamination in the past could have been considerable (Morgan, 1958).

The problem is probably most important in nickel-using industries, where exposures are generally mixed and sometimes rather complex. Thus, stainless-steel welders are also exposed to iron oxide, chromates, nitrogen oxides, ozone and other compounds. Effects on the respiratory system may be related to nickel exposure levels, although not necessarily caused by nickel alone, or perhaps not at all.

1.8.3 Present methods for exposure monitoring

NIOSH (1977; 1982) has recommended standard procedures for personal air sampling and analysis of nickel. Although the routine procedure does not permit the identification of individual nickel compounds, soluble nickel may be leached into a buffered solution, thus allowing estimation of both soluble and insoluble (residual) nickel. Modifications of the NIOSH methods are used under various conditions in Ontario (Acres, 1982). Information on quality assurance procedures has not been found.

The most recent version of the NIOSH method has been validated for airborne nickel levels between 0.57 and 30.7 ug/m^3 (NIOSH, 1982). Low concentrations may be detected by sampling over long time periods, by using a small final volume of solution and by using the most sensitive detection methods. Higher concentrations may be assessed by diluting the solution of dissolved particles. A NIOSH (1977) publication has estimated that compliance with an exposure limit of 0.015 mg/m^3 (15 ug/m^3) could be assessed by technically feasible means.

Assessment of individual nickel compounds would necessitate complicated procedures, such as X-ray fluorescence or X-ray diffraction, and would not be feasible for routine monitoring.

1.9 Conclusions

Nickel is a transition group metal with many useful properties and a wide range of applications in alloys and a large number of compounds. The world's largest deposit of nickel sulfide ore is located in the Sudbury, Ontario, area where it has been mined,

smelted and refined since the beginning of this century. About 16,000 employees are exposed to nickel at the production facilities in Ontario, and at least 9,000 workers are exposed to airborne nickel in the nickel-using industries. In addition, nickel exposures may occur irregularly in several occupations where nickel compounds are used, and dermal exposures are likely to occur rather widely. Current exposure levels are rarely above 0.2 mg/m^3, although certain operations may entail exposures up to 1 mg/m^3. Additional nickel exposures originate from food and drinking-water, including nickel leached from containers and utensils. Past occupational exposures to nickel were much in excess of current levels, but are difficult to evaluate in detail. This problem is of significance, as the delayed health effects seen now are a result of exposures a long time ago. Current methods for monitoring of airborne nickel could be used to assess compliance with exposure limits of about 0.01 mg/m^3 and above.

2. TOXICOKINETICS

The toxicokinetics of inorganic nickel in the body are characterized by the general principle that only soluble Ni^{2+} is absorbed, systemically distributed, and excreted. However, sparingly soluble nickel may be phagocytized by various cell types. Although the knowledge concerning phagocytosis of nickel by cell types other than macrophages and fibroblasts is meagre, various cell types seem to be capable of endocytosis. In biological systems, the Ni^{2+} ion - as well as other metal ions - exists either in particulate form or as various coordination complexes with water or biological or other ligands in the solubilized state. "Soluble Ni^{2+}" is capable of being rapidly translocated in biological systems and is synonymous with such coordination complexes of Ni^{2+}. Translocation between different compartments is often mediated through ligand exchange reactions.

Compared to ions of other toxic metals often encountered in occupational exposure situations (Cd, Pb, Hg, Cu, Zn), the Ni^{2+} ion has a less "soft" character (Andersen, 1984; Nieboer and Richardson, 1980). Consequently, the propensity of Ni^{2+} to form coordination bonds with a high degree of covalent character to biological ligands is less. This property facilitates ligand exchange reactions. The stability constants for coordination complexes generally decrease with decreasing softness of donor and ligand.

The difference in toxicokinetics observed between various nickel compounds is due to the existence of specific coordination species (e.g., salts of Ni^{2+} with chelating agents), differences in the rates of dissolution of particulates, specific exposure and deposition patterns characteristic for particulates, or to the exposure situation itself.

2.1 Routes of absorption

Absorption of nickel in humans may occur as a result of inhalation, ingestion and dermal exposure. As will be reviewed in the following, all three routes have proven important in relation to nickel toxicity in humans. They differ, however, profoundly with regard to 1) the types of nickel compounds of major importance, 2) the fraction of a certain exposure ("dose") which is absorbed, and 3) the toxic effects induced.

Nickel exposure may also take place due to implantation of surgical or dental prostheses. Iatrogenic exposures may also take place during hemodialysis.

The different absorption routes may interplay. Thus, oral intake may cause dermatological response in individuals already sensitized by skin exposure, and gastrointestinal exposure may occur due to mucociliary clearance after pulmonary exposure. However, available evidence indicates that the two most important nickel-associated diseases are caused by exposures from different routes: allergic dermatitis from skin exposure and cancer of the airways from respiratory exposure. Thus, the routes of absorption should be considered separately.

2.2 Pulmonary deposition, clearance and absorption

In the occupational setting, pulmonary exposure is usually the major route of nickel absorption. The pulmonary deposition, clearance, and absorption of nickel particulates follow general principles of lung dynamics outlined below.

2.2.1 General aspects

Pulmonary exposure to particles results in deposition in the naso-tracheal, bronchial, or alveolar regions, depending mainly on physical particle characteristics (size, shape, density, hygroscopicity, electric charge). The deposition also depends on breathing mode (through nose or mouth) and work load (affecting air velocity). Fig. 1 shows the deposition of particles in the airways during nasal (1 A) or mouth (1 B) breathing. Deposition of particles occurs due to impaction, sedimentation, Brownian diffusion, interception or electrostatic precipitation.

Impaction is the main mechanism of deposition for large particles in the upper airways, and is augmented by increased air velocity.

Sedimentation due to gravitational forces is an important mechanism in smaller airways with low air velocity. Sedimentation increases with increasing particle size and residence time, and decreased air velocity.

Brownian diffusion is inversely proportional to particle size and is of importance for very small particles (< 0.5 um) in bronchioli and alveoli. Due to the Brownian motion, these particles may come into contact with the epithelium of the airways. For small particles, transfer from tidal to reserve air space is the major factor affecting deposition.

Interception happens when the edge of a particle touches the walls of the airways and is most important for fibrous materials.

Interception mainly occurs when the fiber length is close to the diameter of the airway.

Electrostatic precipitation may take place during inhalation of charged particles. Aerosolization of aqueous suspensions or solutions often results in generation of charged particles. The enhanced deposition is due either to repulsion forces between similarly charged particles or to image charges induced on the surface of the airways by the aerosol. Experimental studies using aerosols without charge neutralization may thus overestimate the pulmonary deposition of neutral dusts of the same composition. However, freshly fractured mineral dust particles may possess considerable charges and experimental deposition measurements may in this case underestimate the deposition, e.g., in mines, unless due consideration is given to the charge effects.

Cigarette smoking may increase bronchial deposition slightly, and deposition is increased considerably in patients with chronic bronchitis and in some asymptomatic asthmatics. Simple pneumoconiosis does not seem to influence pulmonary deposition significantly. In addition, cigarette smoke contains nickel (section 1.7).

Particles deposited in the bronchial and bronchiolar region are moved upwards by mucociliary clearance and are normally swallowed within 24 h. Exposure to drugs, cigarette smoke, and environmental and occupational pollutants may change the rate of mucociliary clearance significantly.

In the alveolar region, particles may be cleared by phagocytosis, passive transport along surface liquids towards the bronchial tree or dissolution. After phagocytosis, particles in macrophages may be cleared via the mucociliary escalator. Both macrophage-phagocytized and free particles may penetrate the alveolar epithelium, reach the lymphatic circulation and concentrate in pleural, hilar or more distant lymph nodes.

Sparingly soluble particles remaining in the alveoli may become fixed within the parenchymal tissue and remain in the lungs for extended time periods.

Studies of the absorption of deposited particles show that the solubility of the compounds is the main determinant of both the rate and extent of absorption/clearance. While soluble particles deposited in the alveoli may be cleared with a half-life of a few h and systemically absorbed, particles of very low solubility are cleared by a biphasic mechanism. The first phase, lasting several

weeks, consists of the clearance of phagocytized particles, while the kinetics of the slow phase is dependent on the solubility of the particles.

2.2.2 Experimental studies

Williams et al. (1980) found that after intratracheal instillation of ^{63}Ni-labelled $NiCl_2$ (1, 10, or 127 nmol Ni^{2+}/animal) in rats, the variation in clearance rate was not significantly related to the doses. The clearance apparently followed first-order kinetics with a mean rate constant of $1.79 + 0.27 \times 10^{-3}$ min^{-1}. However, in the isolated ventilated and perfused lung, the clearance rate was increased with increasing dose. Ca^{2+} and Mg^{2+} significantly decreased the clearance rate.

In another study of the clearance of intratracheally instilled $NiCl_2$ in rats (1.27 ug Ni/animal) (Carvalho and Ziemer, 1982), 72% and 96.5% of the initial body burden were excreted in the urine after 1 and 21 d respectively. At the same points of time, 29% and 0.1% of the initial burden was present in the lung.

Graham et al. (1978) exposed mice for two h to $NiCl_2$ aerosol of 644 ug Ni/m^3. The lung clearance curve indicated first-order clearance kinetics. Four days post-exposure about 28% of the dose was still present in the lungs. This exposure method more closely resembles conditions encountered in occupational health, and the results may therefore question the validity of the high clearance rates observed in the instillation experiments where, presumably, a considerable fraction is cleared more easily by the mucociliary escalator.

Furst and Al-Mahraq (1981) instilled 50 ug of nickel as the carbonate (solubility, 0.023 mg/ml saline) in 0.02 ml vehicle intratracheally into mice. The urinary excretion indicated that nickel was almost quantitatively cleared within 3 d. This rate is comparable to that observed in the above-mentioned studies of pulmonary clearance of intratracheally instilled nickel chloride.

English et al. (1981) exposed groups of rats to $^{63}NiCl_2$ or ^{63}NiO (prepared by heating $^{63}Ni(OH)_2$ to 250°C for 45 min) by intratracheal instillation (100 nmol Ni/animal). The $NiCl_2$ exposed animals excreted about 63% of the nickel in the urine within 4 d. This figure increased to about 64% after 90 d. The cumulated faecal excretion was about 5 and 6% at these points of time. The half-life in pulmonary tissue was comparable to that observed in the previous studies. In NiO-dosed animals, pulmonary clearance was much slower. At 90 d about 90% of the dose was cleared, and

the faecal and urinary excretion was about 30% each, suggesting extensive GI transfer following the clearance. Both $NiCl_2$ and NiO were rapidly transferred to mediastinal lymph nodes. While $NiCl_2$ was cleared from lymph nodes at the same rate as from lung tissue, the amount of NiO increased in lymph nodes during the experimental period.

Valentine and Fisher (1984) instilled ^{63}Ni-labelled nickel subsulfide intratracheally into mice. A biphasic pulmonary clearance was observed with half-lives of 1.2 and 12.4 d, respectively. The initial rapid phase partially involved mucociliary clearance, since faecal elimination of Ni was significant. After 35 d, about 10% of the dose was retained in the lung. The cumulative urinary and faecal excretion was 60% and 40%, respectively.

Wehner and Craig (1972) exposed groups of Syrian golden hamsters to a NiO aerosol with a particle size of 1-2.5 um MMAD (mass median aerodynamic diameter). The pulmonary deposition, calculated from the integrated exposure and the pulmonary nickel content 3-4 days after the last exposure, when the initial rapid clearing phase was over, was 16.9% after two days of exposure to 73.5 mg/m^3 (group 1) 19.3% after three weeks of exposure to 39 mg/m^3 (group 2) and 19.7% after three months of exposure to 61.6 mg/m^3 (group 3) (mean concentrations of NiO). Animals from group 1 were sacrificed periodically and the pulmonary nickel content measured: after 45 and 100 d about 45% and 30% of deposited NiO was still present in the lung. Another group of hamsters (Wehner et al., 1975) exposed to NiO aerosol for 3 months as group 3 above were also exposed for 10 min to cigarette smoke in a smoking machine twice before and once after the daily NiO exposure. These animals retained 19.2% of inhaled NiO. There was no difference in the tissue content of NiO between smoke-exposed and non-smoke exposed animals: more than 99.7% of the estimated retained quantity of NiO was present in the lungs while 0.21-0.22 and 0.04-0.05% was present in liver and kidneys in both groups.

Kodama et al. (1985) exposed groups of rats to aerosols of green NiO (solubility 0.9 and 2.3 ppm in distilled water, and saline, respectively) (MMAD = 1.2 um) at low and medium dose levels (0.6 and 8.0 mg/m^3) for 140-147 h or 216 h. Animals were sacrificed either at the end of exposure or after a 1-year clearance period. Nickel determination in lung tissue indicated a 14.5% and 19.8% deposition of NiO at the medium and low doses, respectively. Also about 10% of the dose of NiO deposited at the end of exposure had been cleared after 1 year at the medium dose, while 2/3 of the low dose was cleared. The annual clearing rate was 120 and 90 ug

NiO at the medium and low doses, respectively. The nickel concentration in blood was below the detection limit in these groups.

On the basis of these experiments as well as others in which rats were exposed to NiO aerosols with MMAD = 1.2 um at a high dose of 70 mg/m^3, or to aerosols with MMAD = 4.0 um at 0.6 or 70 mg/m^3 for a total of 140 h, Tanaka et al. (1985) calculated the biological half-life of pulmonarily deposited NiO assuming that the clearance rate is proportional to the deposited amount of NiO. Subgroups were sacrificed either at the end of exposure or after a 12- or 20-month clearance period. The half-life depended on the particle size, being 11.5 months for NiO with MMAD = 1.2 um and 21 months for the large particles with MMAD = 4 um. In groups exposed to the high concentration of 70 mg/m^3, nickel concentrations in liver, spleen and blood increased slightly with increasing clearance time.

Kalliomaki et al. (1983 a,b) studied the pulmonary retention and clearance of manual metal arc/stainless steel (MMA/SS) and metal inert gas/stainless steel (MIG/SS) welding fumes in rats. For both types of particles, the pulmonary deposition of nickel was less than expected. After exposure to MMA/SS welding fume, the pulmonary clearance of nickel followed first-order kinetics with $t_{1/2}$ = 30 days. After exposure to MIG/SS welding fume, the clearance of nickel followed a two-compartment model with $t_{1/2}$ = 3 days and 89 days. The iron content of MMA/SS and MIG/SS welding fumes was cleared with $t_{1/2}$ = 40 and 50 days, respectively. These data indicate that some of the nickel content of stainless steel welding fumes are solubilized after pulmonary deposition.

Wehner et al (1979,1981) exposed hamsters to fly ash or nickel enriched fly ash (NEFA), prepared by adding 1 part of nickel acetate to 14 parts of pulverized coal (w/w) before combustion. The nickel in NEFA was apparently not solubilized at any appreciable rate after pulmonary deposition. These studies relate to the toxicokinetics of fly ash rather than nickel, since the toxicity of fly ash was not changed by increased nickel content, and the nickel content of NEFA served merely as a marker measurable by AAS.

Srivastava et al (1984) exposed rats for 6 h/day to 0.2-0.4 mg/l of an aerosol of fly ash which, after collection from the electrostatic precipitator of a coal-fired power plant, had been passed through a 400 mesh sieve. One day after the last exposure, the nickel concentration in lungs, liver, heart, kidneys and small intestine was considerably increased compared to untreated controls. The nickel concentration returned to the control value

within two weeks. The results indicate that some of the nickel content of fly ash may be solubilized after pulmonary deposition.

The experimental investigations on laboratory animals referred to above support the following general conclusions on pulmonary absorption of nickel: 1) deposition in the airways depends on the physical characteristics of the particles inhaled, 2) mucociliary clearance leads to subsequent GI transfer where some absorption may take place, 3) sparingly soluble compounds may be retained in the lungs for long periods of time, and 4) even after pulmonary deposition of large doses of insoluble nickel compounds, the nickel concentration in blood and other body organs are very low.

2.3 Gastrointestinal absorption

Current knowledge related to gastrointestinal (GI) absorption of nickel metal and nickel compounds of low solubility - typically dusts in occupational exposure - is very limited. However, information on other metals would indicate that considerable amounts of nickel metal or sparingly soluble nickel compounds may be ingested without any adverse effects. With nickel, the passage through the acid environment in the stomach with a high chloride concentration could conceivably solubilize nickel from sparingly soluble compounds. This potential is of particular relevance when the nickel is swallowed after pulmonary clearance when the stomach is empty ("between meals").

The studies published on GI nickel absorption in experimental animals or human volunteers relate to water-soluble salts of nickel. Since the biliary excretion of nickel is very low (Marzouk and Sunderman, 1985), quantitation of urinary nickel elimination in combination with either data on the GI dose, or, alternatively, faecal elimination, will allow an approximate estimation of the GI absorption, provided that pulmonary exposure to nickel has been excluded (smokers must be excluded). The minimal GI absorption may be estimated in this way. Thus, faecal nickel elimination is taken to represent the ingested minus the absorbed amount of nickel. Equations I and II indicate the calculations performed.

$$\text{I. Minimal GI absorption} = \frac{\text{cumulative urinary output}}{\text{dose}}$$

$$\text{II. Minimal GI absorption} = \frac{\text{cumulative urinary output}}{\text{cumulative faecal + urinary output}}$$

After a single oral dose of a soluble nickel compound, the plasma concentration increases rapidly and decreases again rather rapidly, while the urinary concentration increases at a lower rate and remains elevated for a longer period (Spruit and Bongaarts, 1977). Thus, to allow calculation of the minimal GI absorption after a single oral dose of nickel, the cumulative urinary nickel excretion should be measured over several days. Even several days after a single dose of nickel, significant amounts are still retained in some body compartments (section 2.7). The total GI absorption is therefore larger than calculated from equations I or II. More precise estimates of GI nickel absorption may be obtained from determination of urinary and faecal nickel output during steady-state conditions in the complete absence of pulmonary nickel exposure.

Gastrointestinal metal absorption is a two-step process: 1) uptake from the intestinal lumen across the brush border membrane into the cytoplasm of mucosa cells, and 2) transport over the basolateral membrane to allow the metal ion to enter the blood stream. The molecular process of GI nickel absorption is not known in detail. However, recent data of Foulkes and McCullen (1986) show that step 1 of the nickel absorption follows first-order kinetics at low concentrations. Saturation of the uptake process begins at 20 umol/l. Although nickel may be an essential element, a specific nickel transport system has not been found as yet, and is unlikely to exist. As with cadmium (Foulkes, 1985) and other non-essential metals or metals required in very small amounts, nickel uptake may be initiated by binding to the brush border membrane; subsequent internalization may occur by means of pinocytosis. Step 2 of nickel absorption follows first order kinetics over a large range of concentrations. Since this process is reversible (nickel is also taken up by epithelial cells from serosal fluid), step 2 most likely consists of passive leakage of a low-molecular-weight nickel complex over the membrane (Foulkes and McCullen, 1986). Mucosal trapping by metallothionein followed by reexcretion into the lumen due to sloughing of epithelial cells is presently believed to be a major defense mechanism towards excessive absorption of zinc and cadmium, and possibly copper and mercury. In contrast, nickel has a very low affinity for metallothionein, and consequently a very small part of nickel is retained in the epithelial mucosal cytoplasm and reexcreted into the lumen (Foulkes and McCullen, 1986).

Ho and Furst (1973) calculated that 3-6% of ^{63}Ni was absorbed in the GI tract following administration of 4, 16 or 64 mg/kg of nickel as $NiCl_2$ by gavage to rats. Christensen and Lagesson (1981) gave a single oral dose (5.6 mg nickel as $NiSO_4 \cdot 6H_2O$) to

adult human volunteers; the cumulative urinary nickel excretion indicated a minimal GI absorption of 3%. Solomons et al. (1982) found that the increase in plasma Ni observed after a single oral dose (5 mg nickel as $NiSO_4 \cdot 6H_2O$) given to fasting human volunteers could be completely suppressed by administration of the nickel dose with a meal; several different beverages also suppressed the increase in plasma nickel. Although this study does not allow calculation of the GI absorption, the data clearly indicate that dietary constituents can prevent the GI absorption (most likely macromolecular chelators such as "fibers", non-absorbable, low-molecular-weight chelators such as phytate, and other metal ions competing for absorption). The results are in agreement with those of Cronin et al. (1980), who showed that fasting human volunteers, given a single, oral dose of nickel sulfate, excreted between 4% and 20% of the dose in the urine after 24 h, indicating a much higher GI absorption than found by Christensen and Lagesson (1981), whose patients were not fasting.

Solomons et al. (1982) also found that EDTA very efficiently prevented GI absorption of nickel. Other investigations have demonstrated that disulfiram and its metabolite diethyldithiocarbamate (DDC) increase the GI absorption of nickel by forming a lipophilic Ni^{2+}-DDC complex (Spruit and Bongaarts, 1977; Lippmann et al., 1980). Thus, certain drugs may promote nickel absorption.

The urinary nickel excretion in 14 nickel dermatitis patients was found to be 1.5 (range 0.4-3.6) ug/day; two weeks after initiation of a diet restricting the oral nickel intake by avoiding a number of food items believed to be rich in this metal, the urinary excretion decreased to 1.0 (range 0.2-2.1) ug/day (Kaaber et al, 1978).

In a number of other experiments, the GI nickel absorption was found to be 1-5% (Horak and Sunderman, 1973; Tedeschi and Sunderman, 1957; Nomoto and Sunderman, 1970). In agreement with these studies, we found a 3-4% absorption of ^{57}Ni as $NiCl_2$ in non-fasting mice in a dose range of 3.3-300 ug Ni/kg body weight (Nielsen et al., 1986).

Collectively, the available data indicate that only a small part of nickel is absorbed when incorporated in a meal. The GI absorption may, however, be much elevated during fasting. Thus, when GI nickel exposure is due to pulmonary clearance, which is a continuous process, the absorption may well be larger than expected.

2.4 Dermal absorption

Water-soluble nickel salts may lead to percutaneous nickel transport. Further, soluble nickel compounds may be released by corrosion of nickel metal and nickel-bearing alloys, or from sparingly soluble compounds due to the action of a range of solutes. Thus, sweat may dissolve nickel, especially due to the chloride content. Also, permanent fluid used by hair dressers, cutting oil and some acids and bases may dissolve small amounts of nickel. The chemical features of the exposure vehicle may profoundly affect the efficiency of dermal absorption: Ni^{2+} in a lipophilic vehicle is likely to be absorbed more rapidly through the skin than Ni^{2+} in a hydrophilic vehicle. Lipophilic organic nickel compounds may pass the dermal barrier rapidly and cause systemic toxicity but are not considered in the present document.

Nickel is absorbed through the appendages of the skin (mainly sweat ducts and hair follicles) at a larger rate than through the epidermis (Wells, 1956). However, the surface area of the appendages is very small. Thus, penetration through the skin is primarily determined by the diffusion rate through the horny layer.

The nickel ion is considered exclusively responsible for the immunological effects of nickel (Wahlberg, 1976). Kolpakov (1963) found that nickel penetrated through the epidermis of cadaver skin and was accumulated in Malpighi's layer, sweat glands, and blood vessels. In Well's (1956) investigation, nickel was found to bind to keratin. Spruit et al. (1965) also found that nickel passed the epidermis of human cadavers and reached the dermis. The penetration of $^{63}Ni^{2+}$ through the stratum corneum of shaved guinea pig skin was investigated by Lloyd (1980): One h after application, nickel had accumulated in keratinaceous areas of stratum corneum and in hair sacs. After 4 h, nickel was present in the stratum granulosum and stratum spinosum, where the Langerhan's cells are located. These cells are involved in the sensitization process preceding the development of nickel-associated contact dermatitis (see section 4.1).

In none of the studies cited above could the fraction of the dose absorbed percutaneously be calculated. About 2/3 of an aqueous solution of $^{57}NiSO_4$ applied on human skin was allegedly absorbed after 24 h; the absorption was similar in Ni-sensitized and nonsensitized individuals (Nørgaard, 1955). More recent confirmation of this result is unavailable, however.

Skin injury or increased water content of the stratum corneum may significantly increase absorption through the skin. Some solvents

and detergents may also increase the percutaneous absorption: the sensitization of Guinea pigs towards nickel due to repeated skin painting was augmented when the skin was painted with an aqueous solution of SDS before the application of nickel (Samitz and Pomerantz, 1958). However, skin painting with ointments containing a macromolecular cation exchange resin (Jarish et al., 1975) or a chelating agent, such as EDTA, DDC or dimethylglyoxim (Kurtin and Orentreich, 1954, Samitz and Pomerantz, 1958), prevented the development of positive patch tests in nickel-sensitive individuals.

Mathur et al. (1977) reported hepatic and testicular lesions in rats after very high dermal exposures to $NiSO_4$. However, this study needs confirmation from independent evidence.

However, low dermal exposures to nickel can lead to sensitisation, and subsequent dermal application (or possibly oral exposure) to very low doses of nickel may provoke contact dermatitis in sensitized individuals. Prevention of occupational nickel dermatitis should focus on the prevention of sensitisation. This requires efficient protection of the skin and low exposure limits for soluble Ni compounds. Percutaneous absorption in humans is unlikely to induce systemic toxicity.

During occupational exposure, particulate nickel compounds may become deposited in the skin or in wounds. The significance of this kind of exposure is unknown.

2.5 Systemic distribution, deposition and excretion

Evidence on absorption of particulate nickel compounds is only available in the case of pulmonary exposure, while absorption of soluble nickel has been demonstrated by all routes. A number of studies indicate that some types of mammalian cells are capable of actively engulfing particles *in vitro* (section 2.9). Due to the lack of knowledge relating to the systemic fate of particulate nickel, this aspect of nickel toxicokinetics will not be addressed in detail here. Soluble nickel may either be absorbed as such or dissolved from particles deposited in specific body compartments (lungs and lymph nodes). Also, several investigations have shown that a number of nickel compounds sparingly soluble in water may be more rapidly solubilized in various body fluids (section 2.9).

2.6 Nickel in blood

Immediately after systemic absorption, nickel is present in blood and then transported to various deposition tissues or rapidly excreted into the urine. During this initial systemic distribution phase, the largest amount of blood nickel is present in serum (Merritt et al., 1984): Between 2 and 24 h after injection of 2 mg $NiCl_2$ in 0.1 ml saline into the thigh of female golden hamsters, the serum nickel concentration was much higher than that in red blood cells, which again was higher than the nickel concentration in white blood cells. Between 6 and 24 h postinjection, the serum nickel concentration was reduced about 40-fold.

Christensen and Lagesson (1981) administered 5.6 mg of nickel as $NiSO_4 \cdot 6\ H_2O$ in lactose to 8 volunteers and followed the whole blood and serum concentrations, as well as the urinary excretion for 3 days. The largest part of blood nickel was present in serum. Serum and whole blood nickel concentrations showed a very high positive correlation ($r=0.99$). The nickel half-life of serum was 11 h (one-compartment model). The serum nickel concentration and urinary nickel excretion also showed a high positive correlation ($r=0.98$). This study indicates that, during oral exposure to soluble nickel, urine seems to be the most useful sample to investigate. It should be emphasized that measurements of nickel in body fluids are poor indicators of exposure to Ni compounds of low solubility.

Nickel in serum is chelated by histidine (HIS), serum albumin (SA), or both in a ternary complex (Mohanakrishnan and Chignell, 1984; Mohanakrishnan et al., 1985; Lucassen and Sarkar, 1979; Glennon and Sarkar, 1982; Hendel and Sunderman, 1972; Callan and Sunderman, 1973; Sarkar, 1984). In several studies the largest part of serum nickel was found associated with SA. It is, however, not certain that SA alone is the major blood transport vehicle for nickel at low serum nickel concentrations. In *in vitro* experiments using human serum, Lucassen and Sarkar (1979) found more than 95% of serum nickel associated with human serum albumin (HSA) when the Ni/SA-ratio was 1. At a Ni/SA-ratio between 0.2 and 0.3, about 85% of serum nickel was associated with HSA. The remaining nickel was almost quantitatively bound to HIS. Less than 0.1% was bound to a high molecular weight protein. The experiment demonstrated a three-fold increase in the HIS-Ni complex due to approximately four times reduction in Ni concentration. The average log (association constants) for the Ni-HSA complex and the ternary Ni-HSA-HIS complex are around 9.57 and 16.23, respectively (Glennon and Sarkar, 1982).

During physiological conditions, the serum concentration of HSA is much larger than the HIS and nickel concentrations. At low serum nickel concentrations, a major part of the nickel may well be transported as the ternary complex. Lucassen and Sarkar (1979), Glennon and Sarkar (1982) and Sarkar (1984) advocated the theory that this ternary complex might facilitate the transport of nickel between separate compartments, conceivably by allowing transfer of nickel to smaller molecules than HSA (HIS itself?), capable of traversing biological membranes.

NMR spectroscopy studies (Laussac and Sarkar, 1980; 1984) have furnished evidence that the nickel transport site of HSA is formed by the three N-terminal aminoacids Asp^1 Ala^2 HIS^3, which seem to be solely responsible for chelation of nickel in a penta-coordinate structure.

A macroglobulin "nickeloplasmin" has been demonstrated to bind nickel in rabbit serum (Nomoto et al., 1971), and a glycoprotein binds a minor fraction of nickel in human serum (Sunderman, 1977; Sarkar, 1984). These nickel-binding proteins may be associated with the essentiality of nickel but are not likely to be of importance in nickel homeostasis at higher serum nickel concentrations, such as are encountered during occupational exposures, where HIS and SA binding most likely dominate (Sarkar, 1984).

2.7 Organ distribution

Nickel seems to be distributed to all organs, in pregnant females even to fetuses (2.8). The kidney is, however, the only organ immediately accumulating appreciable amounts of nickel. Smaller amounts from systemic circulation are deposited in the lungs (higher levels may obviously be reached following inhalation exposures). National Academy of Sciences (1975) tabulated the relative organ distribution of Ni in animal experiments. These data are extended in Table 7. The relative order of organs is given with regard to concentration, not total amount of nickel, and all refer to organ distributions 1/2 - 24 h post-exposure. At times longer than 1 day several studies (Table 8) demonstrated more rapid excretion of nickel from kidneys than from other organs, and continued retention of nickel in the lungs and skin. No organ seems to be a specific depot for nickel.

The different data set in Tables 7 and 8 are in relatively good agreement although different species and administration routes were employed. Also after oral exposure to $^{63}NiCl_2$, the highest organ concentrations of nickel were observed in lungs and kidneys. Taken together, these data indicate that the distribution

of absorbed nickel is relatively independent of the route of entry. The toxicokinetics of nickel can however be significantly changed by administration of chelating agents, e.g. thiuram sulfides and diethyldithiocarbamate (Jasim and Tjalve, 1984; Oskarsson and Tjalve, 1980).

2.8 Transplacental transport

The Ni^{2+} ion is capable of crossing the placenta, and a number of studies have demonstrated embryotoxic and teratogenic properties (see section 5.2).

Schroeder et al. (1964) found increased levels of nickel in still-born mice of mothers who had been exposed to 5 ppm of nickel in drinking water during their entire life span. This observation has received ample confirmation: Lu et al. (1976; 1979) demonstrated placental transfer of Ni^{2+} to foetuses in mice.

Sunderman et al. (1978b) demonstrated by autoradiography and scintillation counting transplacental transport of $^{63}Ni^{2+}$ to fetal tissue in the rat, as did Jacobsen et al. (1978) and Olsen and Jonsen (1979) and Bergman et al. (1980) in mice. Transplacental transport and accumulation of nickel in human foetuses has also been demonstrated (Schneider et al. 1980).

One study (Casey and Robinson, 1978) suggested that nickel levels in the human foetus may be highest during the early prenatal development period. Stack et al. (1976) measured relatively high nickel levels (23 ± 7 ug/g dry weight) in teeth from human still births. These studies, as well as the study by McNeely et al. (1971) of cord blood nickel concentrations in full-term infants convincingly indicate that nickel levels in the human foetus are of a magnitude comparable to that seen in adults, thus indicating that the nickel ion is capable of passing the placental barrier.

2.9 Cellular uptake

Phagocytosis was originally observed as a property possessed by pulmonary, peritoneal, hepatic or circulating macrophages. Recent studies indicate that a number of other cell types are capable of endocytosis under certain conditions: Various types of fibroblasts phagocytize particles, including crystalline nickel compounds (see e.g. Costa and Mollenhauer, 1980a,b). Pinocytosis is an important function of the intestinal epithelium, and recent evidence indicates that bronchial epithelial cells are capable of phagocytic uptake of particles (Haugen et al., 1982). Although

these processes may be of negligible importance in relation to the systemic distribution kinetics of nickel, they may suggest a possible mechanistic explanation for the carcinogenicity of sparingly soluble crystalline nickel compounds, compared to amorphous nickel compounds of similar low solubility. Costa and Mollenhauer (1980a,b) and Costa et al. (1981a,b) demonstrated that cellular transformation (and conceivably carcinogenicity, see section 3.3.7) was related to cellular uptake by phagocytosis: crystalline nickel compounds (alpha forms of Ni_3S_2, NiS and Ni_3Se_2) were all avidly engulfed by Chinese Hamster Ovary (CHO) and Syrian Hamster Embryo (SHE) cells, while amorphous NiS, metallic Ni, Ni_3O_2 and NiO were taken up at much lower rates. The transformation rate after exposure of SHE cells correlated with the cellular uptake rate.

The study of Costa et al. (1981a) demonstrated preferential phagocytosis of particles with diameter 2-4 um. Manganese dust and the Mn^{++} ion reduced both phagocytosis and transformation to a similar degree. The enhanced cellular uptake of crystalline nickel compounds is related to the surface charge: Abbrachio et al. (1982a) and Heck and Costa (1983) found that noncarcinogenic, nontransforming, amorphous NiS particles (which are not phagocytized) had a positive surface charge, while carcinogenic, transforming, avidly phagocytized crystalline NiS, Ni_3S_2 and NiO all had negative surface charges. Reduction of the positive surface charge of amorphous NiS with $LiAlH_4$ increased both the rate of phagocytosis by CHO cells and the transformation frequency after exposure of SHE cells (Costa et al. 1982).

Uptake of particles by the fibroblast-like cell types, CHE cells and CHO cells must be discriminated from phagocytosis by macrophages: NiO and metallic nickel which were only sparingly taken up by CHO cells (Costa et al., 1981a) were both avidly phagocytized by rat peritoneal macrophages <u>in vitro</u>: Kuehn et al. (1982) found a strong positive correlation between the dissolution half-times in rat serum and phagocytic indices for 17 nickel compounds; alpha-Ni_3S_2 was an exception to this concordance, since it was rapidly phagocytized despite it had one of the shortest dissolution half-times.

Nickel subsulfide was rapidly solubilized during incubation in a solution containing DNA, rat liver microsomes, and NADPH, and the solubilized Ni^{2+} ion was apparently octahedrically coordinated in a ternary complex with DNA and protein (Lee et al., 1982). Alpha-Ni_3S_2 was more soluble in rat serum than in water (Kasprzak and Sunderman, 1977). Metallic nickel was dissolved by incubation in horse serum, or muscle or other tissue homogenates (Weinzierl and

Webb, 1972) as well as in human serum (Ung and Furst, 1983). Solubilized nickel was bound mainly to small diffusible molecules (Weinziel and Webb, 1972).

Kuehn and Sunderman (1986) compared the dissolution rates of 17 particulate nickel compounds in water, rat serum, and rat renal cytosol. While four compounds were not solubilized within the experimental period, the dissolution half-time of one compound was equal in all three media. Eleven of the compounds were solubilized more rapidly in renal cytosol and serum than in water. The dissolution half-time for the last compound could not be assessed due to precipitation of solubilized nickel. The dissolution half-time of alpha-Ni_3S_2 (34 and 21 days in serum and renal cytosol) agreed with the excretion half-life of alpha-Ni_3S_2 *in vivo* after intramuscular injection into rats.

Internalized nickel particles are preferentially localized close to the nuclear envelope. However, unsolubilized particles do not enter the nucleus (Costa et al. 1981b). While intracellular nickel is mainly found in extranuclear organelles after exposure to soluble nickel (Herlant-Peers et al., 1983), exposure to crystalline Ni_3S_2 or NiS results in high concentrations of nickel in the nucleus (Webb et al., 1972; Jasmin and Riopelle, 1976). Phagocytized particulate nickel is solubilized relatively rapidly (Abbracchio et al., 1982b) and then binds strongly to nuclear material (Costa et al., 1981b). Nickel also binds to isolated chromatin and to chromatin in isolated nuclei *in vitro* (Ciccarelli and Wetterhahn, 1985). Nickel is capable of interacting with the tubulin-microtubule system, and thus to affect the function of the spindle (Roychaudhury et al., 1982; Andersen, 1985, Swierenga and Basrur, 1968).

Phagocytosis followed by cytoplasmic dissolution may therefore deliver much higher doses of the Ni^{2+} ion close to the genetic material than exposure to soluble Ni^{2+}, which would induce considerable toxicity before a higher intracellular concentration could be achieved. As described in section 3.3.5 Sen and Costa (1985) observed selective fragmentation of the heterochromatic long arms of the x-chromosome after Ni^{2+} exposure due to the generation of high cytoplasmic nickel concentrations during dissolution of NiS particles.

A number of studies have demonstrated that nuclear components of mammalian cells seem to have a high affinity for the Ni^{2+} ion. Data describing the subcellular distribution of nickel, after exposure either to soluble nickel compounds or to readily phagocytized crystalline nickel compounds of low solubility, should

therefore be evaluated bearing in mind the possible creation of artifacts due to preferential binding of nickel to specific subcellular components during the preparational steps following the exposure of integrated whole organisms or cell systems to various nickel compounds.

At present no evidence is available which indicates that endocytosis of particles takes place in nasal and pulmonary epithelial tissues during occupational exposure to particulate nickel compounds. It is therefore not possible to evaluate whether slow solubilization of pulmonarily deposited particulate nickel leading to chronic exposure of surrounding tissues, or endocytosis followed by cytoplasmic dissolution is the critical factor for the high carcinogenicity of sparingly soluble nickel compounds, as compared to soluble nickel.

Renal handling of nickel is quantitatively of major importance in relation to nickel toxicokinetics. Low molecular weight nickel complexes as well as nickel bound to SA are efficiently extracted from serum and excreted in the urine. Several nickel-binding proteins have been identified in kidney cytosol (Abdulwajid and Sarkar, 1983; Oskarsson and Tjalve, 1979b; Sunderman et al., 1981a; 1983a; Behari et al., 1984).

Using HPLC, agarose gel electrophoresis and sephadex G-200 chromatography of renal cytosol from ^{63}Ni-treated rats, Sunderman et al. (1981a; 1983a) identified one major nickel-binding protein with MW < 5000, and five minor peaks with MW from 7000 to > 130,000. Abdulwajid and Sarkar (1983) reported a nickel-binding glycoprotein in rat renal cytosol with MW 15,000-16,000, and 10% carbohydrate content. This protein was suggested to be a part of the renal basement membrane involved in transmembrane metal transport (Abdulwajid and Sarkar, 1983).

Several nickel-binding proteins have been identified in other tissues (pulmonary: Herland-Peers et al., 1983; Oskarsson and Tjalve, 1979b; liver: Herland-Peers et al., 1983; Oskarsson and Tjalve, 1979b; Behari et al., 1984). Our present knowledge about the function of nickel-binding components in tissue cytosol is, however, still meagre.

2.10 Excretion

Excretion of systematically absorbed nickel may take place through sweat (Hohnadel et al., 1973; Christensen et al., 1979), hair and faeces (see section 2.3). These routes are, however, normally of minor importance compared to urinary nickel excre-

tion. After parenteral administration of $^{63}NiCl_2$ to rats, the cumulative urinary and faecal excretion of nickel was 77.94% and 4.87%, respectively, during 6 d after i.p. exposure (Tandon, 1982), and 89.8% and 3.0% during 4 d after i.v. exposure (Sunderman and Selin, 1968 %). After i.m. administration of $^{63}Ni_3S_2$ to rats, the cumulative urinary and faecal excretion during 8 weeks was 67% and 7%, respectively (Sunderman et al., 1976).

After intratracheal instillation of $^{63}NiCl_2$ into rats, 96.5% of the dose was excreted in the urine after 21 d (Carvalho and Ziemer, 1982), while the cumulative urinary and faecal elimination of nickel after 90 d was 64.3% and 6.4% in another study (English et al., 1981).

Marzouk and Sunderman (1985) followed the biliary excretion of i.v.-administered $^{63}NiCl_2$ in the rat by bile duct cannulation and bile collection. The cumulative biliary nickel excretion was calculated to be < 0.5% during the first 24 h post dosage. A very high biliary nickel concentration (62 ug/g) was observed at autopsy after an acute lethal nickel intoxication: A 2 1/2 years old girl died 4 h after having swallowed about 15 g of nickel sulfate crystals (Daldrup et al., 1983). Even when assuming this high concentration in 250 ml bile which represents the cumulative 24 h biliary excretion inadults, nickel excretion in bile would still be much less than 1% of the dose. Thus, biliary excretion is likely to be of negligable importance compared to renal excretion.

2.11 Conclusions

Nickel in the body exists as sparingly soluble compounds retained in the lungs and lymph nodes, and as systemically distributed coordination complexes of absorbed nickel. The pulmonary deposition, retention, clearance and absorption are governed by the physico-chemical properties of the particles and aerosols. Dermal absorption is limited but is of significance for nickel-allergic patients. Gastrointestinal absorption of soluble nickel compounds is usually about 2-5%, but may be more when the stomach is empty. In the blood, nickel is mainly located in the serum after absorption, and most of the nickel is bound to albumin. Relatively much nickel is transferred rapidly to the kidneys, from which it is subsequently excreted. Lesser amounts are transferred to the lungs and the skin where, on the other hand, the retention time is longer.

Tissue and body fluid concentrations of nickel are elevated considerably after pulmonary exposure to soluble compounds, while

undetectable or only slight elevations result from exposure to sparingly soluble nickel compounds. Such compounds may be taken up especially by phagocytes in particular crystalline nickel compounds with a negative surface charge, such as nickel subsulfide. The genotoxic activity of the nickel compounds may be related to the rate of cellular uptake. Also, compounds sparingly soluble in water may be more rapidly solubilized in cytosol and serum, and the intracellular distribution of nickel may be different from that resulting from uptake of soluble nickel compounds. The genotoxic potential is likely to be related to these properties.

3. CARCINOGENICITY

3.1 Background

Since the early 1930s, research on nickel carcinogenesis has progressed greatly. At the beginning of this period, a high incidence of cancer of the nasal cavities and lung was noted among workers at a nickel refinery in Wales, U.K. (National Academy of Sciences, 1975; Evans et al., 1974; Bjornerem et al., 1983). The exposure of these workers was very complex and included in particular different compounds of nickel, copper, arsenic, sulfur and iron. Thus, the exact etiology of the cancer cases was hard to evaluate. Since then, research in this area has dealt with a range of experimental approaches as understanding of carcinogenesis has improved, and epidemiological studies have attempted to characterize the causative exposure in more detail.

In the absence of definite knowledge concerning the carcinogenic effect of specific nickel compounds in humans, long-term animal experiments can provide evidence of the carcinogenic potential of individual nickel compounds. The animals are observed for their full lifespan, or a major part thereof, and the development of neoplastic lesions recorded, subsequent to or during exposure to various doses of the nickel compounds tested.

Extrapolation from animal data to human exposure is fraught with difficulties because of differences, especially in metabolic pathways and susceptibility among and within the species. Therefore, the fate and effects of nickel and nickel compounds should preferably be examined in the individual species at the organism level, at the organ level and at the cellular level.

In vitro models aim at imitating the processes which occur in the organism (*in vivo*); the advantage of these *in vitro* models is that they offer the possibility of studying the mechanisms more closely in carcinogenesis systems of lower complexity. Because of the lack of complexity of simple systems, extrapolating from *in vitro* studies to humans entails even more difficulties than extrapolating from animal studies to humans.

During recent years, as reviewed by Sunderman (1984), remarkable progress has occurred in the understanding of nickel carcinogenesis and several hypotheses for the molecular pathogenesis of nickel carcinogenesis have ensued. Suggested mechanisms for induction of somatic mutations by nickel include:

(1) Ni may bind covalently to DNA, causing strand breaks and excision of nucleotides, leading to frame-shift mutations during DNA repair.

(2) Ni may form DNA-protein crosslinks, causing aberrant DNA replication or repair, and disturbing mitosis.

(3) Ni may cause B-DNA to Z-DNA transition, altering chromatin structure and perhaps derepressing oncogenes.

(4) Ni may impair fidelity of DNA replication by reacting with substrate-binding or catalytic sites of DNA polymerase, disturbing complementary base-pairing.

(5) Ni may bind to histones, non-histone nuclear proteins, or RNA, influencing chromatin structure, and possibly modifying phosphorylation of regulatory proteins.

Available information does not allow substantiation of one or more of the mechanisms listed as responsible for the development of a transformed cancer cell. Also, current evidence may suggest that the Ni^{2+} ion is responsible for the effects, although the possible significance of Ni^{3+} still needs to be clarified.

3.2 Criteria for carcinogenicity

Before discussing the existing literature on genotoxicity, carcinogenicity in experimental animals and carcinogenicity in epidemiological studies, the existing criteria for evaluating carcinogenic potential should be briefly reviewed.

The International Agency for Research on Cancer (IARC, 1982) has developed a classification of evidence for carcinogenic potential. First of all, epidemiological evidence is scrutinized.

Studies in experimental animals are classified according to the following major criteria: "sufficient evidence of carcinogenicity, indicating an increased incidence of malignant tumours (a) in multiple species or strains; (b) in multiple experiments (preferably with different routes of administration or using different dose levels); or (c) to an unusual degree with regard to incidence, site or type of tumour, or age at onset; additional evidence may be provided by data on dose-response effects, as well as information from short-term tests or on chemical structure." These criteria only refer to the strength of the experimental evidence that a chemical is carcinogenic and neither to the extent of its carcinogenic activity nor to the mechanism

involved (IARC, 1982).

Similarly, sufficient evidence of genotoxicity in short-term tests requires: "at least three positive results in at least two of three test systems measuring DNA damage, mutagenicity or chromosomal effects; when two of the positive results relate to the same genetic effect, they should be derived from systems of different biological complexicity" (IARC, 1982).

On the basis of the three sets of data, a summary evaluation of carcinogenic risk to humans was developed by IARC (1982). Chemicals, groups of chemicals, industrial processes or occupational exposures are classified as carcinogens, probable carcinogens or possible carcinogens without sufficient information. Although nickel has been evaluated by IARC (1976), the wealth of more recent data should also be taken into account.

3.3 Genotoxicity

3.3.1 Effects on nucleic acids in cell-free system

In section 2.9 on cellular uptake and subcellular distribution these intracellular processes were considered of importance for genotoxic potentials. In this section the literature on nickel-binding to genetic material is reviewed. Table 8 summarizes investigations of genetic material exposed to nickel *in vivo* and *in vitro*, the effects being studied *in vitro* in cell-free systems.

Although the Mg^{2+} ion is the natural activator for DNA polymerase, Sirover and Loeb (1976a; 1976b) showed that nickel ions also can activate DNA polymerase *in vitro* but only with a maximum rate of nucleotide incorporation of 7% of that achieved with magnesium.

Miyaki et al. (1977) used nickel ions as the activating factor for *E.coli* DNA polymerase I and found an enhanced misincorporation of all four nucleotides compared to the situation where magnesium was used. Further, nickel increased misincorporation even in the presence of magnesium. Studies with more than 40 different metals (Sirover and Loeb, 1976a; Tkeshelashvili et al., 1979; 1980) show a good correlation between the ability of certain metal ions to enhance infidelity of DNA synthesis and the mutagenic or carcinogenic effect. This finding suggested the hypothesis that the mutagenic and carcinogenic effects of nickel could be related to the capacity of the nickel ion to enhance infidelity of DNA synthesis.

However, the exact mechanism by which certain divalent metal ions decrease the fidelity of DNA synthesis in vitro is not known. Zakour et al. (1981a; 1981b) reviewed recent work in this field and proposed three possible explanations: 1) altered conformation at the substrate-binding site of DNA polymerase; 2) altered conformation at the catalytically active site of DNA polymerase, possibly involving allosteric transition produced by interactions of the metal ion with the enzyme at loci distant from the active site; and 3) altered base-template specificity, interfering directly with complementary base-pairing during DNA replication. As the most likely mechanism the authors suggest the ability of nickel to substitute for magnesium as polymerase activator.

Niyogi et al. (1981) studied the effect of nickel chloride and 13 other metal chlorides on the transcription of calf thymus DNA and phage T4 DNA with E.coli RNA polymerase and found that nickel chloride increased RNA chain initiation rate at very low concentrations. At increasing concentrations, a progressive decrease in initiation rate was seen when overall transcription was inhibited.

Studies on DNA transcription by Wang et al. (1979; 1981) demonstrated that DNA, which is normally found as a right-handed double-helix called B-DNA, can, under certain conditions, adopt a left-handed double helical form (Z-DNA). They also studied the structure of Z-DNA and found that Z-DNA regions are especially rich in guanine and cytosine residues.

Van de Sande et al. (1982) showed that nickel ions were able to induce transition of guanine- and cytosine-rich B-DNA regions (poly-(dG-dC)) to Z-DNA. This transition could be reversed by chelating nickel ions with EDTA.

Bourtayre et al. (1984) further showed that the four nickel compounds, nickel chloride, nickel sulfate, nickel carbonate and nickel subsulfide were all able to induce transition of B-DNA to Z-DNA at concentrations of 0.4 mmol/l equal to 24 ug Ni/ml. Liquier et al. (1984) showed that an antitumour drug called SOAZ was able to stabilize B-DNA, thus preventing B-Z transition even when the concentration of nickel was raised by ten-fold. Nickel and other carcinogens could conceivably act at regulatory regions of DNA to induce imbalance between the B and Z forms of DNA, and thereby distort normal transcriptional activity. One further effect of such changes could possibly be the induction of erythropoiesis after intrarenal nickel injection (section 6.4).

3.3.2 Mutagenicity in microorganisms

Mutagenesis assays with phages and bacteria have, with the exception of a few special cases, proven to be incapable of detecting nickel as a mutagen. Table 9 summarizes studies of mutagenesis in microorganisms. All investigations were performed with soluble nickel compounds ($NiCl_2$ and $NiSO_4$). Tests were negative in the Salmonella reverse mutation assay, in the E.coli WP2 fluctuation test, the Bacillus recombination assay and a bacteriophage assay.

In contrast, Pikalek and Necasek (1983) found that nickel ions exhibit a mutagenic effect on a homoserine-dependent bacteria strain, Corynebacterium sp. 887, in both a simplified fluctuation test and a so-called clone method. In the concentration range from 0.031 to 0.25 ug/ml (7.7-62 ng Ni/ml), nickel chloride did not produce any revertants but at concentrations of 0.5, 1.00, 5.0, and 10.0 ug/l (0.12-2.5 ug Ni/ml), dose-related increases in the number of revertants were obtained. As the number of revertants increased, cell survival decreased.

Furthermore, LaVelle and Witmer (1981) claimed that $NiCl_2$ was mutagenic in the Salmonella typhimurium TA 1535 assay; however, since details of experimental data are not available, a critical evaluation of this study is not possible. Tweats et al. (1981) found $NiCl_2$ positive in a differential killing assay based on a repair-deficient strain of E.coli.

Singh (1983; 1984) studied induction of gene conversion and reverse mutation by nickel sulfate in a eukaryote assay with Saccharomyces cerevisiae. In the first study, $NiSO_4$ gave a positive response for reversion. In the second study, Singh found that at much lower concentrations, $NiSO_4$ did not induce any reverse mutation but gave a weak positive response for conversion. It must be added that the nickel salt was cytotoxic, resulting in a survival rate between 39-70% at the concentrations tested.

3.3.3 Mutagenicity in mammalian cells

Three reports deal with mutagenic effects of nickel in vitro in mammalian cells (Table 10). All studies were positive, but two used essentially the same technique, and Miyaki et al. (1977) and Hsie et al. (1984) expressed some reservations with regard to their results. Miyaki et al. (1977) had difficulties in detecting the mutations induced because of considerable cytotoxicity of the nickel ion. Hsie et al. stated that their findings need

confirmation since mutagenicity testing is influenced by variations in ionic composition of the medium and the physiological state of the cells during treatment. The third group, Amacher and Paillet (1980), found that nickel ions were mutagenic in the LS1784/TK+/- mouse lymphoma assay and observed a dose-related increase in the mutation frequency. The cell survival at the concentrations used ranged from 5% to 49%.

3.3.4 Induction of DNA lesions and repair

Investigations concerning induction of DNA lesions and DNA repair are summarized in Table 11. Two related studies by Ciccarelli et al. (1981) and Ciccarelli and Wetterhahn (1982) describe the effect of $NiCO_3$ administered i.p. to rats. Kidney, liver, lung and thymus gland nuclei were examined at 3 to 20 h after treatment. Single-strand breaks, DNA-protein and DNA-interstrand crosslinks were found in kidney nuclei; single-strand breaks were found in lung nuclei. No DNA-damage was observed in liver and thymus nuclei. A dose-response relationship both for single-strand breaks and crosslinks was observed in kidney nuclei. Time-course studies suggested the presence of an active repair mechanism in the nuclei, as the degree of DNA damage decreased again with time of examination after treatment. Maximal DNA damage in kidney occurred at 2 to 4 h following injection. The levels of DNA damage and repair were found to correlate with nickel concentrations in tissue and cells. Although this evidence suggests that nickel may cause DNA lesions, other studies (section 2.9) indicate that very little nickel enters the cell nuclei. Thus, the preparation methods could possibly result in exposures of DNA to nickel under conditions which differ from *in vivo* circumstances.

Robison and Costa (1982) and Robison et al. (1982; 1983; 1984) have investigated the ability of soluble $NiCl_2$ and three insoluble nickel compounds (crystalline Ni_3S_2 and NiS, and amorphous NiS) to induce single-strand breaks and DNA-repair synthesis in Chinese hamster ovary cells (CHO cells) and in Syrian hamster embryo cells (SHE cells). Their results for three of the compounds corresponded well with the results obtained by Ciccarelli and Wetterhahn (1982): the soluble $NiCl_2$ and the insoluble crystalline Ni_3S_2 and NiS all induced single-strand breaks and DNA-repair, whereas the insoluble amorphous NiS resulted in neither single-strand breaks nor induction of DNA repair. In the case of $NiCl_2$ and crystalline NiS, the effect was shown to be both time- and dose-dependent. The lack of activity of amorphous NiS may be related to the observation that amorphous compounds are phagocytized only slowly (section 2.9).

Fornace (1982) investigated the ability of $NiSO_4$ to produce single-strand breaks in cultured human fibroblasts and found that no single-strand breaks were induced, whether or not the DNA polymerase activity was inhibited by the addition of 1-beta-D-arabinofuranocylcytocine hydroxyurea. This study used very high doses compared to the above mentioned studies.

3.3.5 Chromosomal damage

The clastogenic effect of different nickel compounds has been investigated in vivo and in vitro as shown in Tables 12 and 13, respectively. In particular, these assays have been used for studying lymphocytes from nickel-exposed workers.

Waksvik and Boysen (1982) studied two groups of workers exposed mainly to dry dust of NiO and Ni_3S_2 at the Falconbridge nickel refinery in Norway. Peripheral lymphocytes showed a statistically significant increase in chromosome gaps in two groups of exposed workers. No statistically significant relationship was found between the increase of gaps and plasma concentration of nickel, length of exposure or age of the workers. The number of breaks found did not differ significantly from that of the controls.

In another paper by Waksvik et al. (1984) a group of retired nickel refinery workers was matched with controls never exposed to nickel. A statistically significant increase in both chromosome breaks and gaps was found. The exposed group had been exposed for more than 25 years to nickel concentrations in the air above 1 mg/m^3, levels which were higher than in the previous study.

Studies of clastogenic effects in experimental animals are listed in Table 12. Mathur et al. (1978) studied bone marrow and spermatogonial cells; Jacquet and Mayence (1982) examined embryonic cells derived from treated male germ cells; and Deknudt and Leonard (1982) used the micronucleus and dominant lethal test. In none of these studies was a clastogenic effect of a nickel found (only soluble nickel compounds were tested). However, a toxic response on male germ cells and on preimplantation zygotes was shown (Jacquet and Mayence, 1982; Deknudt and Leonard, 1982) (section 5.1). Since the experimental animal studies on clastogenic effects were performed with rather high doses (10-50% of LD_{50}) and only at one or two dose levels, the clastogenic potential of nickel compounds cannot be evaluated from these studies.

In vitro studies of clastogenic effects are listed in Table 13. Umeda and Nishimura (1979) and Nishimura and Umeda (1979) studied the clastogenic effects of four nickel compounds: $NiCl_2$, $(CH_3COO)_2Ni$, $K_2Ni(CN)_4$ and NiS and found no effect of $NiCl_2$ and $(CH_3COO)_2Ni$, a slight increase in both chromosome breaks and gaps after exposure to NiS and an increase only in gaps after exposure to $K_2Ni(CN)_4$. All four compounds tested produced cytotoxicity at the levels used. When the exposure period was followed by a recovery period, all four nickel compounds induced chromosomal aberrations. At the maximum rate, 20% of the metaphase cells showed clastogenic effects. Investigation of the protein, RNA and DNA synthesis during exposure showed considerable decreases in DNA and protein synthesis and only a slight decrease in RNA synthesis at the exposure levels used. The authors suggested that the delay in expression of chromosomal aberrations may be due to cytotoxicity, which blocks the growth of the cells. After removal of nickel, the cells recovered and were able to enter mitosis.

Larramendy et al. (1981) tested nickel sulfate for clastogenic effects at a single concentration and found damage in about 10-15% of cells tested, i.e., human lymphocytes and SHE cells. The concentration tested was lower than the concentrations used in the studies mentioned above.

Sen and Costa (1985), found that crystalline NiS and $NiCl_2$ caused chromosome gaps and breaks in CHO cells in a time- and concentration-dependent fashion. Chromosomal aberrations induced by $NiCl_2$ occurred randomly among the autosomal arms; however, the heterochromatic centromeric regions of the chromosomes were preferentially damaged. In addition to the types of aberrations induced by $NiCl_2$, crystalline NiS particles also caused selective fragmentation of the heterochromatic long arms of the X chromosomes. The authors attributed this difference in fragmentation to the mechanism of delivery of nickel ions from phagocytized crystalline NiS particles. They aggregate around the nuclear membrane and release large amounts of nickel ions near the heterochromatin which is localized at the inner surface of the nuclear membrane. The cellular uptake dissolution of nickel are discussed in section 2.9.

3.3.6 Sister chromatid exchange

Nickel compounds have been tested for the ability to induce sister chromatid exchange (SCE) in a variety of systems, in vivo and in vitro (Table 14). In two human studies by Waksvik and Boysen (1982) and Waksvik et al. (1984), an increased rate of

SCE was not found in peripheral lymphocytes from workers occupationally exposed mainly to nickel oxide and nickel subsulfide in the nickel refining process. One group of workers examined was exposed for more than 25 years to nickel concentrations in the air, above 1 mg Ni/m^3.

In vitro studies have been performed in cultured human lymphocytes, mammary carcinoma cells from the C3H mouse, SHE cells and CHO cells. The studies listed in Table 14 show an increased SCE rate after exposure to soluble compounds (nickel chloride, nickel sulfate, nickel acetate and potassium cyanoniccolate) and sparingly soluble compounds (nickel sulfide and nickel subsulfide). The studies varied with regard to concentration and treatment time. The concentrations ranged from 10^{-6}M to 10^{-3}M (0.06 - 59 ug Ni/ml) and the treatment time ranged from 2 h followed by a recovery period to a continuous exposure for 72 h.

Wulf (1980) found a positive dose-response relationship for SCE induction in human lymphocytes exposed to $NiSO_4$. Also, a dose-response and a treatment-time-response relationship for SCE were found by Sen and Costa (1985) in CHO cells exposed to crystalline nickel sulfide and nickel chloride. On the other hand, a dose-response relationship for nickel subsulfide was sought but not found by Saxholm et al. (1981).

3.3.7 Cellular transformation

The transforming capacity of nickel compounds has been tested in various cell systems. Established cell lines that possess a labile marker of neoplastic transformation may be used. In the cell lines C3H/10T 1/2 and Balb 3T3, a positive test is indicated by the appearance of dense foci of cells on a confluent monolayer of non-transformed cells. Similarly, in the BHK-21 cell line, a positive test is indicated by the formation of anchorage-independent cell colonies in a semisolid growth medium. Cell transformation assays can also be performed with freshly isolated primary cultures of SHE cells which exhibit essentially normal growth parameters. This latter assay has been further developed to detect a number of different characteristics and stages of cellular transformation, such as changes in growth control, changed morphology and loss of contact inhibition. Finally, transformed clones may be tested for malignancy by transplantation into a suitable host animal. Table 15 summarizes recent studies of cellular transformation induced by nickel compounds.

Saxholm et al. (1981) found that concentrations as low as 0.001 to 0.1 ug/ml (0.0007 - 0.07 ug Ni/ml) of nickel subsulfide in-

duced formation of transformed foci of cells in cultured C3H/10T 1/2 cells. Similarly, Hansen and Stern (1983) demonstrated anchorage-independent growth of BHK-21 cells after exposure of the culture to sparingly soluble nickel subsulfide and nickel oxides (NiO, Ni_2O_3), to the soluble nickel acetate ($Ni(CH_3COO)_2$) and fume from MIG welding with a pure nickel wire. They found a wide range of transformation potentials at the same dose of nickel per area of culture, but all substances induced the same number of transformed colonies at the same degree of toxicity (e.g., 50% survival). From these results the authors suggest that if cytotoxicity is a direct measure of intracellular nickel concentration, the nickel ion must be the ultimate transforming agent, independent of source or uptake mechanism.

This theory is further supported by studies of Lechner et al. (1984) using normal human bronchial epithelial (NHBE) cells: After 40 days in vitro exposure of NHBE cell cultures to 5-20 ug/ml $NiSO_4$ (1.1 - 4.5 ug Ni/ml) followed by up to 35 days culture in nickel-free medium, colonies of mitotic cells arose at an average rate of about 1 per 100.000 exposed cells. Such colonies were not observed in control cultures or cultures exposed up to 90 days to <5 ug/ml $NiSO_4$ (1.1 ugNi/ml). Although 12 isolated cultures upon expansion into mass cultures were non-malignant when injected into athymic nude mice and still revealed anchorage-dependent growth, they did show various early transformation characteristics: Some had increased population-doubling potential, others showed aberrant terminal squamous differentiation, and still others had lost requirement for epithelial growth factor for clonal growth.

One study was performed with normal human bronchial epithelial cells continuously exposed to nickel sulfate for 40 days. After an incubation period, colonies appeared containing cells with a changed morphology and growth control. As none of the cells in the culture showed anchorage independency nor was able to produce tumours when transplanted into athymic nude mice, the observed transformation was not a complete neoplastic transformation.

The remaining studies in Table 15 were performed with cultured SHE cells but with different test models. Costa et al. (1978) showed that $NiSO_4$, $NiCl_2$, crystalline nickel selenide (Ni_3Se_2), crystalline Ni_2S_3 and crystalline NiS were positive, whereas amorphous NiS was shown to be nearly negative or negative. Nickel sulfate was found to induce loss of contact inhibition, i.e., marked cellular growth and unequivocal overlapping of cells (DiPaolo and Casto, 1979), and to enhance the transformation of

SHE cells by adenovirus (SA 7) (Casto et al. 1979a; 1979b). Costa et al. (1982) tested $NiCl_2$ for the ability to induce loss of contact inhibition and found that nickel chloride was about one-third to one-half as effective as crystalline NiS calculated on a weight basis. Costa (1979) showed a concentration-dependent incidence of transformation for crystalline compounds (Ni_2S_3 and Ni_3Se_2). Costa et al. (1979) also showed that clones of alpha-Ni_3S_2-transformed cells were able to develop undifferentiated local sarcomas when injected subcutaneously into nude mice, the ultimate test for neoplastic transformation.

Both particle size, crystallinity and surface charge are important characteristics of particulate nickel compounds, determining the propensity of the particle for being phagocytized by cells, such as CHO cells and SHE cells, and phagocytosis correlates with *in vitro* transforming activity and carcinogenic potency in experimental animals (as reviewed in detail in section 2.9).

Other factors may be of importance in the expression of nickel-induced carcinogenicity. Thus, Costa et al. (1978), added manganese to primary cultures of SHE cells at the same time as alpha-nickel subsulfide. Transformation was prevented compared to similar cultures where alpha-nickel subsulfide was added alone. Manganese may also prevent cancer development after nickel injection in experimental animals (section 3.4.5). Rivedal and Sanner (1980; 1981; 1982) found a synergistic enhancement of transformation frequency for the combined treatment of nickel sulfate with three organic carcinogens (benzo(a)pyrene (BP), N-hydroxy-2-acetylaminofluorene, and 4-nitroguinoline-1-oxide). Moreover, the synergistic effect of the combined treatment with nickel sulfate and BP did not require that the two compounds be present at the same time, since the transformation frequency was also enhanced when nickel sulfate was added after the cells had been exposed to BP. This result may indicate a promotor effect of the nickel ion. Similarly, Rivedal et al. (1980) demonstrated a synergistic effect of nickel sulfate and cigarette smoke extract. When added simultaneously to cultured SHE cells, 3-4 times as many transformed colonies were observed as expected from additivity of the effects of the individual exposures.

3.3.8 Histological changes in human tissue

Studies on cellular transformation indicate that nickel compounds are able to transform cells either to true neoplastic cells or to cells otherwise transformed. This observation raises the question whether transformed cells or histologically changed cells can be

found in humans exposed to nickel compounds (clastogenic effects and sister chromatid exchange has already been dealt with in sections 3.3.5 and 3.3.6).

McEwan (1978) studied sputum cytology in workers from a nickel-sintering operation at INCO: 583 men participated in the program, and 1385 samples collected on three successive days were examined. Moderate or more severe dysplasia of epithelial cells was found in approximately 10% of the samples, and malignant cells or suspected malignant cells were found in 16 men. These 16 men were examined continuously; a tumour was localized in 9 cases, in some cases after many months.

Torjussen et al. (1979b) studied biopsies of nasal mucosa taken from former and present employees at the Falconbridge Nickel Refinery in Norway and from controls. Histological changes of the epithelium were graded according to a point score table. Four cases of nasal carcinoma and 18 cases of epithelial dysplasia were found in the exposed group in contrast to none among the controls. Statistical analysis indicated that high histological scores correlated with working in departments with crushing, roasting, smelting and electrolysis as well as with age and length of nickel exposure.

A similar, subsequent study by Torjussen et al. (1979a), examined 318 active and 15 retired nickel workers employed for at least 18 years. Two workers from the roasting and smelting departments had nasal carcinoma, 12% of the active and 47% of retired workers had epithelial dysplasia, and only one of 57 controls, a male carpenter, had dysplasia. Epithelial dysplasia is considered to be a precancerous lesion. Stratified cuboidal epithelium with loss of ciliated cells and development of squamous epithelium were seen in all groups, but in significantly higher frequency in the nickel-exposed groups. Duration of nickel exposure, type of nickel-refining work and tobacco consumption were the independent variables that had the highest explanatory values for histopathological changes. The authors suggest that a continuous change exists from pseudostratified epithelium, cuboidal and mixed cuboidal/squamous epithelium to dysplasia as stages in the development of neoplastic growth in nasal mucosa.

This sequence of epithelial changes can also be distinguished in three connected studies performed in workers at the same nickel refinery in Norway by Boysen and Reith (1982a,b,c). Scanning electron microscopic and light microscopic analyses revealed that the epithelial transition is accompanied by a stepwise enlargement of the basal cells and their nuclei and nucleoli as well as

a stepwise alteration in several independent subcellular components, i.e., a change in mitochondria with a threefold increase in size and corresponding reduction in number as well as a decrease of crista surface density at 32% from pseudostratified epithelium to dysplasia. Furthermore, surface density of rough endoplasmatic reticulum increased by 100%, the volume fraction of tonofilaments decreased by 60% and the number of desmosomes increased with 60%. These morphological changes, especially those involving the mitochondria and endoplasmatic membranes, suggest that biochemical differences between the specific stages may occur.

Boysen et al. (1984) found that the degree of hyperplastic changes in nasal mucosa was larger among retired nickel workers than among a control group of the same age, the changes being largest among electrolysis workers, in workers with a long employment and in smokers. The changes were inversely related to the duration of retirement.

These studies on human cells from workers exposed to nickel dusts confirm the carcinogenic potential indicated by the experimental studies *in vitro*.

3.3.9 Conclusions

Genotoxic effects of nickel ions *in vitro* have been demonstrated by several means. Studies have shown effects on the genetic material in cell-free systems and mutagenicity in some microorganisms, but not in others, as well as in cultured mammalian cells. Chromosomal damage, sister chromatid exchange and cellular transformation have also been documented, some of these effects even in cultured human cells. Although dose-response relationships have been obtained in several studies, these are difficult to translate to human exposure situations. The effects have been caused by sparingly as well as by easily soluble nickel compounds, and the magnitude of the effects may be related by the degree of cellular toxicity and perhaps the intracellular nickel concentration. Sparingly soluble, crystalline compounds may exert particularly intensive effects in phagocytic cells due to their rapid uptake. Thus, although the nickel ion may to be the ultimate carcinogen, the concentration at the cellular target is difficult to predict when complicated by different uptake and solubilization kinetics.

3.4 Carcinogenicity in Experimental Animals

3.4.1 Design of carcinogenicity assays

Tests of nickel compounds for induction of neoplastic tumours in experimental animals can be performed in a number of ways of different significance and interpretation.

The sensitivity of carcinogenicity assays employing administration routes, such as intraocular, intramuscular, intrarenal or intratesticular may be much higher than the sensitivity of assays employing routes of direct relevance to human exposure. Results of such studies where suspensions of particles are deposited in the tissue, should generally be carefully evaluated to assure that a positive result is not due to "foreign body carcinogenicity" or "solid state carcinogenicity". As reviewed by Theiss (1982), it is generally agreed that such tumours arise due to nonspecific tissue reactions rather than chemical carcinogenesis. Further, although a variety of histological types have been found, foreign body carcinogenesis almost exclusively results in tumours which seldomly metastasize (Johnson et al., 1970; Ott 1970). Induction of local tumours may only be considered evidence for a general carcinogenic potency of the compound in humans if distant tumours have been induced as well, either after the same or other parenteral administration routes, or after administration via routes relevant for human exposure (Theiss, 1982).

Injection of suspensions of various nickel compounds into a number of different tissues have been shown to induce very high frequencies (up to 100%) of cancers (sarcomas) at the site of injection. However, as opposed to tumours induced by foreign body carcinogenicity, these tumours sometimes metastasize, and in some cases distant primary tumours have been obtained (Sunderman, 1981b; 1984). Further, pulmonary exposure has resulted in tumour induction. The combined evidence from animal experiments concordantly indicate that nickel is a potent carcinogen.

Sunderman (1983) evaluated several carcinogenicity studies of nickel subsulfide (Ni_3S_2) from his own laboratory, involving more than a thousand animals and performed with similar protocols under uniform conditions. The tests included several species and strains of rodents, diverse routes of administration and various doses. No absolute species specificity for Ni_3S_2 carcinogenesis appears to exist although rats seem to be more susceptible to nickel subsulfide than mice, hamsters or rabbits. A significant difference has been found between various strains, with the following ranking of four rat strains in susceptibility to in-

duction of renal neoplasms after intrarenal injection of nickel subsulfide: Wistar-Lewis > NIH Black > Fischer > Long-Evans Hooded rats. Furthermore, the administration regimen may influence the results obtained. From studies with Fischer rats, the following ranking occurs for susceptibility of organs to tumour induction after direct injection of Ni_3S_2: muscle > testis > kidney > liver. Other factors likely to influence carcinogenicity in experimental animals are age and sex of the animals, dose of the compound tested and the length of observation time after treatment.

General guidelines for the performance of a good carcinogenicity study in experimental animals have been recommended. In principle, the whole assay should be designed to resemble the human situation as much as possible with regard to exposure route, duration of exposure and observation time. Additionally, the conditions should be optimized with regard to the possibility of cancer development. In the 1960s the U.S. National Cancer Institute introduced the term "maximal tolerated dose" (MTD) which is a dose inducing some toxicity, e.g., changes of enzyme levels in the blood, or less than 10% loss of weight. This dose should be used as the maximum dose in a carcinogenicity study (NCI, 1976; OECD, 1981). Further, the substance should be administered as early in the stage of growth as possible to increase the sensitivity of the assay, since the promotion step during malignant transformation and cancer development require several cell divisions. Thus, OECD (1981) recommended to start administration of the test substance to the animals before they are 4-6 weeks old. After exposure, the animals must be observed for their entire life span, i.e., 18 months for mice and 24 months for rats, as the latent period for tumour development often is very long.

3.4.2 Administration via the respiratory system

Experimental animal studies testing nickel compounds administered via the respiratory system are very relevant in relation to risk evaluation for occupational nickel exposures. However, exposure chambers and instrumentation for inhalation experiments are very expensive and the studies laborious. Thus, only limited evidence is available.

The first notable studies in this field, with the reservation that the experimental procedures were inadequate according to current guidelines, were published by Hueper (1958) and Hueper and Payne (1962). They found that continuous inhalation of finely powdered metallic nickel (<4um) resulted in the development of multicentric adenomatoid formations in the alveoli and hyperplas-

tic proliferations of the terminal bronchiolar epithelium in guinea pigs and rats. Furthermore, they found that intrapleural implantation of powdered nickel in rats elicited cancers in about one third of the animals, whereas intrapulmonary deposited nickel powder produced pulmonary sarcoma in only one of 34 rats.

More recently, Ottolenghi et al. (1974) exposed 226 Fischer 344 rats by inhalation of about 1 mg of Ni_3S_2/m^3 for 78 weeks (6 h/d, 5 d/week). The exposed group showed a significantly increased incidence of pulmonary hyperplastic and neoplastic lesions originating from the bronchial and bronchiolo-alveolar segments. The overall incidence of lung tumours in the animals treated with nickel subsulfide was 14% compared with 1% in the controls.

Wehner et al. (1975) exposed 102 Syrian golden hamsters to 53 mg of NiO/m^3 (7 h/d, 5 d/week) by inhalation for 61 d. The nickel oxide as well as the sham exposure did not result in any carcinogenic effect.

Yarita and Nettesheim (1978) studied the effect of nickel subsulfide on respiratory tract mucosa. They obtained tracheas from donor animals, tied each to a polyethylene tube and transplanted them under the dorsal skin of isogeneic recipients, using two tracheas per rat (Fischer 344). Four weeks after implantation of the tracheas, at a time when the tracheas were well vascularized and fully established with a normal mucosa, Ni_3S_2 was inserted in doses of 1 or 3 mg in gelatin pellets. Tumours were produced in 15% (5% sarcomas and 10% carcinomas) of the tracheas exposed to 1 mg of Ni_3S_2 and in 70% (68.5% sarcomas and 1.5% carcinomas) of the tracheas exposed to 3 mg of Ni_3S_2. The authors emphasized this relatively low carcinoma incidence for a substance that is highly suspected of being a major etiological agent in respiratory carcinoma development in workers exposed to nickel. They tried to explain this finding as follows: 1) high and early sarcoma incidence, 2) high toxicity of Ni_3S_2 with epithelial necrosis and 3) synergism with other factors involved in the causation of respiratory tract cancers in nickel workers.

Nickel induce a number of toxic effects in the respiratory tract (section 6.3), and this local toxicity could be of importance with regard to promotion of cancer development.

3.4.3 Oral administration

Oral administration is also relevant to the human situation. The daily intake of nickel with diet and drinking water is in the order of 100-1000 ug nickel/day (section 1.7), and part of oc-

cupationally inhaled nickel particles is cleared by the mucociliary system from the respiratory system to the pharynx and then swallowed (section 2.2.1).

Schroeder et al. (1964) administered 5 ppm (mg/l) nickel in drinking water to 50 Charles River mice of each sex. The mice were observed for 36 months, i.e., until all animals had died. About 32% of the animals were lost due to cannibalism and other causes. Seventeen per cent of the male mice and 9% of the female mice died because of tumours compared to 25% and 37%, respectively, in the control group, a result which may appear to be a negative test for nickel as a carcinogen. On the other hand, the experiment was not described in sufficient detail to allow any detailed evaluation according to the criteria mentioned above.

In another investigation performed by Sunderman et al. (1978a), Syrian golden hamsters of the LVG/LAK strain were treated with alpha-nickel subsulfide by painting the mucosa of each cheek pouch three times weekly. None of the animals treated developed malignant neoplasms in the cheek pouches, oral cavity or gastrointestinal tract. As the number of animals in each group treated was low and the mortality ratio in the groups was rather large, this experiment cannot be used as a negative test for nickel carcinogenicity.

Thus, neither of the two tests of oral administration of nickel compounds allows any conclusion to be drawn concerning the carcinogenicity by this route of administration

3.4.4 Intraperitoneal injection

Stoner et al. (1976) tested nickel acetate in the strain A mouse lung adenoma induction assay. The principle of the test is that 30 weeks after initiation of consecutive i.p. injections of a carcinogen at the maximal tolerated dose, the number of lung adenomas observed at autopsy may be increased in carcinogen-treated animals compared to vehicle-treated controls (Shimkin and Stoner, 1975). The morphologically benign adenomas arise from alveolar epithelial cells and may with time develop into malignant, metastasizing cancers. Thus, a massive cumulative dose of nickel acetate (360 mg/mouse administered in 24 injections) induced a significant increase in the number of adenomas/mouse (1.26 ± 0.29 s.e. compared to 0.42 ± 0.10 in the vehicle treated controls). Half of this dose did not increase the tumour yield.

Poirier et al. (1984) found that the nickel-induced increase in lung adenoma formation in strain A mice could be completely

prevented by coinjection of Ca^{2+} or Mg^{2+} at molar ratios of 1:1 or larger. This result corroborates and extends the results of Sunderman et al. (1976) that magnesium prevents nickel subsulfide-induced rhabdomyosarcomas in rats upon intramuscular coinjection, and again points to the Ni^{2+} ion as the causative agent in nickel carcinogenesis.

3.4.5 Intramuscular injection

Studies of carcinogenic effects after intramuscular injection of nickel compounds are listed in Table 16.

Sunderman and Maenza (1976) studied the carcinogenicity of four insoluble nickel-containing powders: amorphous nickel monosulfide, nickel subsulfide, partially converted nickel-iron sulfide matte, and metallic nickel, all with particle diameters less than 2 um. They were administered i.m. to Fischer rats at two dose levels, 60 and 240 umol of nickel/rat (3.5-14 mg Ni/rat). Whereas alpha-Ni_3S_2 was highly carcinogenic, amorphous NiS did not induce any tumours. Furthermore, the carcinogenic potency of partially converted nickel-iron sulfide matte was less than alpha-Ni_3S_2 but greater than Ni powder. No differences were found between the proportions of various histological types of sarcoma that developed at the injection site in any of the experimental groups. Of 28 tumours that occurred, 50% were classified as fibrosarcomas, 32% as rhabdomyosarcomas, 11% as undifferentiated sarcomas and 7% as pleomorphic sarcomas. Metastases to lungs, mediastinal lymph nodes or retroperitoneal lymph nodes were found in 43% of the sarcoma-bearing rats.

Similar results were found by Sunderman et al. (1978a), Sunderman (1979) and Yamashiro et al. (1980) with hamsters, albino mice and different strains of rats exposed to nickel subsulfide in concentrations ranging from 2.5 to 10 mg/animal.

Sunderman (1979), further derived a dose-response curve for induction of sarcomas in male Fischer rats and found that sarcoma incidence at 62 weeks after injection was linearly related to the reciprocal of the alpha-Ni_3S_2 dose, and ranged from 24% in rats receiving 0.63 mg to 100% in rats receiving 20 mg. This study showed no indication of a threshold dose for the induction of sarcomas. Out of 336 tumours in tumour-bearing rats, 48% were rhabdomyosarcomas, 27% undifferentiated sarcomas, 21% fibrosarcomas, 3% liposarcomas, 0.6% neurofibrosarcomas and 0.3% haemangiosarcomas. Metastases were found in 41% of the tumour-bearing rats. This distribution of tumour types differs from the one mentioned above with regard to the relative number of fibro-

sarcomas and rhabdomyosarcomas.

The carcinogenic potential of six different nickel compounds, metallic nickel dust, crystalline forms of nickel selenides (Ni_3Se_2 and NiSe) nickel sulfides (alpha-Ni_3S_2 and alpha-NiS) and amorphous nickel sulfide was studied by Sunderman et al. (1979b). Equal doses (14 mg Ni/rat) of the compounds were given i.m. to male Fischer rats. Based upon the marked differences in sarcoma incidence after administration of crystalline alpha-NiS (14/14 = 100%) and amorphous NiS (0/10 = 0%), the authors concluded that the physical form of nickel sulfide has a critical influence upon their carcinogenic activities. Additionally, the crystalline nickel compounds were all found to be very potent carcinogens in this experiment, although the sulfides seemed to be more potent than the selenides.

Focusing on the physical form of nickel compounds, Kasprzak et al. (1983) studied the carcinogenic potential of colloidal, air-dried and crystallized nickel hydroxide ($Ni(OH)_2$) injected into Wistar rats and found weak evidence that air-dried (5/20) and crystallized nickel hydroxide (3/20) produced local tumours, in contrast to the colloidal form (0/20). Studies on in vitro solubilization rates of the same compounds in human blood, serum, artificial lung fluid and ammonium acetate buffer (pH 7.4) showed an increase from crystalline to air-dried to colloidal forms. Relating this finding to the solubilization rate of highly carcinogenic nickel subsulfide, the solubilization rates of all the nickel hydroxide forms are higher than that of nickel subsulfide. The authors finally pointed out that an inverse relation may exist between the tumour yield and rate of solubilization of the compounds tested (see also section 2.9).

Sunderman and McCully (1983a) tested nickel arsenides (NiAs, $Ni_{11}As_8$, Ni_5As_2, NiAsS), nickel antimonide (NiSb) and nickel telluride (NiTe) for carcinogenicity in male Fischer 344 rats after i.m. administration. As indicated in Table 15, all the compounds tested except one, i.e., NiAs, were carcinogenic to rats, Ni_5As_2 and NiAsS being the most potent compounds. The apparent lack of carcinogenic effect of NiAs is remarkable because it is described as having chemical and physical properties that closely resemble those of crystalline nickel sulfides and selenides (NiS, Ni_3S_2, NiSe and Ni_3Se_2). Out of 99 tumours found in this study, 68% were rhabdomyosarcomas, 11% fibrosarcomas, 15% osteosarcomas, 1% fibriohistolytic sarcomas and 5% undifferentiated sarcomas; this distribution differs from the histological types mentioned above.

Since the sensitivity of cells to carcinogens is greater at high growth rates, transplacental carcinogenicity of nickel subsulfide was tested by Sunderman et al. (1981b). Twenty mg of Ni_3S_2 was administered i.m. into 8 pregnant Fischer rats on day 6 of gestation. The progeny, comprising 50 offspring (17 males and 33 females), were followed for 26 months: no significant effect upon tumour incidence in the progeny was found. The only effect observed was a decreased body weight of progeny of Ni_3S_2-treated dams when compared to progeny of control dams. Ni_3S_2 is relatively insoluble in water, but it gradually becomes solubilized following i.m. injection in rats, with progressive conversion to Ni_7S_6, NiS and $Ni(OH)_2$ and eventual liberation of Ni(II) into body fluids. The present study was designed so that the fetuses would be exposed to nickel ions and possibly other dissolved products of Ni_3S_2 (i.e., Ni_7S_6, NiS and $Ni(OH)_2$) throughout the period of organogenesis. Furthermore, the pups were nursed by their own dams, which would result in exposure through colostrum and milk.

Four studies concern the effect of a nickel compound combined with other compounds. Sunderman et al. (1974) gave a single i.m. injection containing Ni_3S_2 dust (2.5 mg) alone or in combination with equimolar amounts of aluminium, copper, chromium or manganese dusts. They found that the addition of manganese dust to Ni_3S_2 dust significantly depressed Ni_3S_2-induced tumourigenesis at the dose level tested. This finding may relate to the protection of manganese against nickel-induced cell transformation in vitro (section 3.3.7).

Subsequently Sunderman et al. (1976) studied the effect of Ni_3S_2 combined with manganese and chromium more closely at a lower dose level (1.2 mg of Ni_3S_2). The incidence of sarcomas within 2 years after injection of Ni_3S_2 plus manganese was 7% versus 77% in rats that received only Ni_3S_2 and 80% in rats that received Ni_3S_2 plus chromium (1.0 mg). Furthermore, the authors noted that the admixture of manganese diminished the in vitro solubility of $^{63}Ni_3S_2$ in rat serum, serum ultrafiltrate or water. In vivo studies showed that ^{63}Ni concentrations in ultrafiltrates of supernatant fractions of homogenates of injection sites were significantly lower (about half) at 5 to 6 months after injection in the group treated with both Ni_3S_2 and manganese as compared to the group treated with Ni_3S_2 alone. Admixture of manganese with NiS_2 did not affect the mobilization or excretion of Ni, nor did it alter the acute pathological reactions to Ni_3S_2.

In a third study on combination effects of Ni_3S_2 and manganese, Sunderman and McCully (1983b) found that the inhibition of

alpha-Ni_3S_2 carcinogenesis by Mn dust is a local rather than a systemic effect. It was shown by the fact that inhibition was observed only when Ni_3S_2 and manganese dust were injected i.m. simultaneously whereas no inhibition was seen when the rats received injections of Ni_3S_2 in one thigh and of manganese dust in the opposite thigh. Four manganese compounds, MnS, Mn_2O_3, MnO_2 and $Mn_2(CO)_{10}$ with respective valences of 2, 3, 4, and 0, were also tested. Combined administration with Ni_3S_2 did not reduce the sarcoma incidence compared with the group receiving Ni_3S_2 alone. However, MnS seems to have a slight inhibitory effect, as the median tumour latency period and the median survival period were significantly longer in this group.

Finally, Kasprzak et al. (1985) investigated the effects of calcium and magnesium salts administered by three different routes (oral, multiple s.c. injections and injection simultaneously with Ni_3S_2) on the formation of muscle tumours by nickel subsulfide in Fischer 344 rats. They found that magnesium carbonate in contrast to calcium carbonate inhibited the activity of Ni_3S_2 by decreasing the yield and increasing the latency of the local muscle tumours when injected i.m. together with Ni_3S_2. Histological examination of the injection site revealed that the admixtures of calcium carbonate or magnesium carbonate to Ni_3S_2 did not affect the mobilization of nickel from the injection site. They did, however, influence the cellular responses to Ni_3S_2 in early stages (3 d to 22 weeks). Magnesium carbonate, unlike calcium carbonate, strongly decreased the necrosis and increased macrophage proliferation at the Ni_3S_2 injection site besides delaying the occurrence and proliferation of histiocytic-stromal cells, and preventing the occurrence of altered myoblasts.

3.4.6 Intrarenal injection

As indicated in Table 17, Jasmin and Riopelle (1976) and Jasmin and Solymoss (1978) injected 5 mg of nickel subsulfide, nickel sulfide or metallic nickel dust into each pole of the right kidney of Spraque-Dawley rats. In three experiments performed with Ni_3S_2, renal carcinomas were found in 44-55% of the rats, as opposed to experiments performed with NiS and metallic nickel where no carcinomas were found. The animals were only observed for 12 months, but the frequency would be unlikely to increase between 12 and 24 months. The carcinomas were fairly well demarcated in the early stages. They invaded the renal parenchyma and extended through the hilar region or bulged on the surface of the kidney. The neoplastic renal cells showed a pronounced tendency to evolve toward an anaplastic, spindle-cell variant.

Studies by electron microscopy suggested an epithelial origin.

Sunderman et al. (1979a) compared the susceptibility of various strains of rats to an intrarenal injection of Ni_3S_2. Male Fischer rats showed an intermediate susceptibility and were chosen for further investigations of the effects at various dose levels. In rats that received an intrarenal dose of 0.6, 1.2 or 2.5 mg of Ni_3S_2, no renal cancers were found in contrast to the groups that received 5 or 10 mg Ni_3S_2, where a dose-response relationship for renal cancers was found. The induction of renal cancers was inhibited in rats receiving 10 mg of Ni_3S_2 and 6.9 mg of manganese dust (Mn) by intrarenal injection.

Seventeen nickel compounds were tested by Sunderman et al. (1984) and Sunderman and Hopfer (1983) for carcinogenic effect after intrarenal injection of 7 mg Ni/kidney in Fischer 344 rats. The compounds included nickel sulfides (amorphous and crystalline NiS, alpha-Ni_3S_2 and NiS_2), selenides (NiSe, Ni_3Se_2), arsenides (NiAsS, NiAs, $Ni_{11}As_8$, Ni_5As_2), oxides (NiO), antimonide (NiSb), telluride (NiTe), titanate ($NiTiO_3$), ferronickel alloy and metallic nickel dust. Tumours were caused by 9 of the compounds tested, their potential being ranked as follows: crystalline alpha-NiS (57%), alpha-Ni_3S_2 (27%), NiS_2 (20%), NiAsS (20%), NiSe (8%), Ni_3Se_2 (8%), $NiFeS_4$ (8%), NiFe alloy and NiAs (5%). The renal cancers included eight fibrosarcomas, five mesangial cell sarcomas, two renal cell carcinomas, two carcinosarcomas, two leiomyosarcomas, two undifferentiated sarcomas, one rhabdomyosarcoma and one nephroblastoma. Comparing these results to the results obtained by injecting the same 17 nickel compounds intramuscularly into male Fischer rats as earlier described (section 3.4.5), the authors found a significant rank correlation between the incidences of the two data sets. Rank correlation was also observed between the incidence of erythrocytosis and renal cancers in the 17 nickel-treated groups. Erythrocytosis, defined by peak hematocrit values that averaged more than 55% during 1-4 months after i.r. injection, was found in groups of rats exposed to the following 9 compounds mentioned with the mean peak hematocrit in parentheses in ranked order: alpha-Ni_3S_2 (76 ± 2), crystalline alpha-NiS (75 ± 4), NiS_2 (73 ± 9), NiSe (73 ± 8), $NiFeS_4$ (73 ± 4), Ni_3Se_2 (71 ± 9), nickel dust (68 ± 8), NiO (67 ± 14), NiAsS (62 ± 7)). However, no significant rank correlations were observed by comparing the incidences of renal cancers and the following parameters: nickel mass-fractions, dissolution half-times in rat serum or renal cytosol or phagocytic indices of the compounds in rat peritoneal macrophages.

The association observed between erythrocytosis (section 6.4) and carcinogenesis in rats following i.r. injection of nickel compounds does not necessarily mean that the two phenomena are linked in their pathogenesis. Various explanations were reviewed and discussed by Sunderman et al. (1984), one being that the association possibly reflects differences in intracellular bioavailability of nickel ions, influenced by the complex interplay of chemical reactivities, surface properties, and extracellular or intracellular dissolution kinetics of the nickel compounds. Another explanation for the association may be that enhanced expression of the erythropoietin gene occurs during renal carcinogenesis by nickel compounds. This hypothesis is based upon analogy to the enhanced expression of the alpha-foetoprotein gene that occurs in rats during hepatocarcinogenesis by N-2-fluorenylacetamide. As mentioned in section 6.4, enhanced erythropoietin production may be a marker of dedifferentiation or neoplastic transformation (Sunderman et al., 1984), and this possibility is consistent with the following observations: 1) erythropoietin-mediated erythrocytosis has been reported in numerous patients with neoplasms of the kidney and certain other tissues, 2) plasma erythropoietin concentrations are increased in rats with renal carcinomas induced by dimethylnitrosamine and 3) erythropoietin is produced by specific neoplastic cell lines. Finally, Sunderman et al. (1984) point out that the inhibition by manganese dust of alpha-Ni_3S_2 induction of both erythrocytosis and carcinogenesis may constitute indirect evidence that the two effects share a common initiating mechanism.

3.4.7 Other routes of administration

Implantation has been used as an experimental model for testing the carcinogenicity of metallic nickel: After s.c. implantation of nickel pellets to Wistar rats, local fibrosarcomas were induced (Mitchell et al, 1960). This result may be explained as foreign body carcinogenesis, but i.m. injection of fine nickel powder (< 2 um particle size) likewise resulted in sarcoma induction (Sunderman and Maenza, 1976). These results are especially relevant in relation to the widespread use of nickel-containing orthopedic implants that may generate wear particles. Also, occupational dusts may get trapped in cuts or wounds.

Damjanov et al. (1978) investigated the acute and carcinogenic effects of nickel subsulfide injected intratesticularly into Fischer rats. Acute effects included development of dose-dependent necrosis of testicular tissue. In this study, 16 out of 19 rats (84%) developed malignant testicular sarcomas within 20 months after an injection of 10 mg of Ni_3S_2. The sarcomas were

characterized as fibrosarcomas (63%), malignant fibrous histocytomas (19%) and rhabdomyosarcomas (19%). The occurrence of rhabdomyosarcomas in the testes, which is normally devoid of striated muscle, suggests that the rhabdomyosarcomas were induced by malignant transformation of undifferentiated, pluripotent mesenchymal cells. Metastases to lung, kidney and/or abdominal lymph nodes were found in 4 of the 16 tumour-bearing rats. Damjanov et al. noted the following advantages of the intratesticular administration route: the injection site is localized and encapsulated; the testis is easily palpabable, which means that small tumours can be readily detected; and the possible differentiation of rhabdomyoblasts from undifferentiated mesenchymal cells may be studied.

Albert et al. (1982) studied the carcinogenic effect of 0.5 mg of alpha-Ni_3S_2 injected into the vitreous body of the right eye of Fischer rats. They found that malignant tumours developed in the injected eyes of 14 out of 15 rats within 8 months. Altogether, 21 eye tumours developed, including melanomas (52%), retinoblastomas (19%), cyliomas and unclassified malignant neoplasms (14%). Three of the melanomas resulted in extraocular extensions and one metastasized to lungs and brain. Although the melanomas arose from amelanotic uveal melanocytes, melanosomes were observed in the tumour cells. As a procedure to test the carcinogenicity of nickel compounds, intraocular injection has the advantage of short latency period, high tumour incidence and ease of tumour detection.

3.4.8 Conclusions

Nickel compounds, in particular alpha-nickel subsulfide have been used as model compounds in carcinogenesis research. The scientific studies in this area have resulted in a large number of papers of major interest. Unfortunately, the studies deal primarily with mechanisms of carcinogenesis and development of animal models, rather than prediction of cancer in relation to occupational and environmental exposures. Thus, the evidence dealing with pulmonary and oral exposure to nickel is limited and does not satisfy the requirements for carcinogenesis assays. However, a series of studies using intramuscular and intrarenal injection suggests that several nickel compounds are carcinogenic and that the potential varies for different compounds. Further, intrarenal injection of several nickel compounds results in two events which appear to be related: development of carcinoma and stimulated erythropoiesis, perhaps both being a result of cellular dedifferentiation or neoplastic transformation. Although the kinetics of nickel in the body and within the cells are not understood to

a sufficient degree, this evidence again points to the nickel ion as the ultimate carcinogen. However, the evidence available does not allow any firm conclusions to be drawn concerning human exposure settings.

3.5 Epidemiological Studies

3.5.1 Interpretation of epidemiological data

Epidemiology is a scientific discipline which deals with the occurrence of human disease, in particular with regard to risk indicators. Epidemiology incorporates both statistical and medical aspects. However, in dealing with more-or-less well-defined disease entities, possibly of heterogeneous or composite causation, occurring in heterogeneous human populations with a non-uniform exposure history, epidemiology is not an exact science. One cannot realistically expect that epidemiological studies will be able to gauge, in a precise fashion, the extent to which different factors have caused a particular disease (ACOHOS, 1983). However, with information from other scientific fields, (sections 3.3 and 3.4), epidemiology may add knowledge of considerable significance for the prevention of disease.

Most epidemiological studies in relation to occupational exposures to nickel are historical, prospective cohort studies, i.e., a group of workers employed within a certain period has been followed and the total mortality and causes of death are compared to those occurring in a reference group, or the numbers calculated from national or regional rates. In addition, several studies have used the case-control design, where the exposure history is compared between a group with the disease under study and a similar group without the disease. Further, a few studies have used other designs, mainly variations of the designs mentioned above.

The quality of an epidemiological study depends on a range of factors (Doll et al., 1981): first, the right study population must be available, and it must be large enough to distinguish the effects of a specific hazard from the effects of random variation of small numbers or, alternatively, to give confidence that no material risk exists when negative results are obtained. Second, the follow-up period must be sufficiently long to allow for the latency period for cancer or other disease which may only be detected several years, often decades, after the onset of exposure. Third, the extent of exposure, the speciation and the occurrence of other exposure factors during the study period should be known. Fourth, when cancer incidence is examined,

account must be taken of the fact that mortality data does not accurately reflect the risk of developing tumours with a low fatality rate, and that the reliability of death certificates depends, e.g., on the autopsy frequency. Finally, potential confounding variables such as smoking habits and other occupational exposure, must be considered.

A general framework for evaluation of historical prospective cohort studies has been delineated by the Advisory Council (ACOHOS, 1983). These criteria may, to some extent, also be applied in epidemiological studies of other design. The criteria for evaluating the quality of historical prospective cohort studies include:

1) Definition of the study cohort

   a) Method of selection
   b) Criteria for inclusion or exclusion
   c) Size of the cohort

2) Quantification of exposure

   a) Detail in work history files
   b) Extent of industrial hygiene data
   c) Quality of industrial hygiene data
   d) Consideration of confounding factors

3) Ascertainment of mortality

   a) Quality of follow-up technique
   b) Completeness of follow-up
   c) Availability of death certificates or other records to determine the cause of death
   d) Length of follow-up

4) Analysis of results

   a) Suitability of the external control group
   b) Availability of an internal control group
   c) Allowance for latency effects
   d) Use of appropriate statistics
   e) Demonstration of an exposure gradient
   f) Discussion of possible biases

With regard to the epidemiological studies on occupational nickel exposure, several important problems should be emphasized, as they relate to several studies reviewed on the following pages.

1) Mortality prior to the follow-up period: in some studies, the population examined had been exposed during a considerable time interval, while mortality, for practical reasons, was assessed only during a more recent time period. In such cases, deaths may have occurred before the follow-up period started, and the cohort examined could therefore represent a subgroup of "survivors" with a better mortality record.

2) Insufficient information on past exposures: a major disadvantage to historical prospective studies is the lack or limited extent of exposure data. Detailed measurements have only been carried out recently, and extrapolation to past conditions is difficult or, perhaps, impossible because changes in work procedures have occurred. This problem relates to the magnitude of exposure, the particular speciation and the possible occurrence of confounding exposures, as described in further detail in sections 1.8.1 and 1.8.2.

3) Misclassification of exposure groups: in studies of nickel refinery workers, each individual has in several cases been classified according to the job longest held. However, in one study an individual was counted in each of the exposure categories according to the jobs held, while length of employment and relationship to the latency of disease were not taken into account. An additional method of classification gave employment in a particular department (calcining) priority. As the true nature of the carcinogenic factor or factors remains unknown, the validity of these classifications is difficult to evaluate, and a number of possibilities may have to be explored in the search for a consistent pattern. Additional problems of possible misclassification may occur in studies of Ontario nickel production workers. Many of these individuals may previously or subsequently have worked in another nickel facility or otherwise been exposed to potential carcinogens. In particular in the Sudbury, Ontario, area, a man with experience from one company or one particular process would have a high chance of being hired by another company or moved to a related process. Thus, the cohorts examined may overlap considerably, thereby causing possible misclassification bias.

4) Other occupational exposures: workers with experience from nickel mining and processing would be likely to seek employment in similar industries when not working with nickel. Thus, these workers may be exposed to other carcinogenic factors, unrelated to nickel. In the Sudbury area, for example, other employment is limited, and some workers may have worked in the Elliott Lake

uranium mines, either before or after employment with a nickel-producing company. Other work-related exposures could constitute an important confounding variable.

5) Insufficient follow-up: the follow-up of the cohort must be as complete as possible and extend over a sufficient span of years to allow for a considerable latency period. Incomplete follow-up is usually due to such factors as emigration. If the survival of the individuals not traced is different from that of the remaining cohort, the results obtained from the study may be misleading. Further, if follow-up covers only a short time period, most of the man-years accumulated will be "empty", and a group of successfully employed males will often exhibit a mortality lower than expected for the first several years after first employment. On the contrary, employees first hired much earlier may exhibit a relatively larger excess mortality. This phenomenon causes so-called lead-time bias.

6) Ascertainment of cause of death: information from death certificates is frequently imprecise. Thus, cancer of the nose and nasal sinuses may be classified as bone cancer or nasopharyngeal cancer, or perhaps not even mentioned as cause of death. Laryngeal cancer rates obtained from death certificates are also unreliable because of the low mortality rate, and morbidity information from cancer registries are therefore preferable. Incomplete ascertainment of the disease under study may result in bias.

7) Validity of reference population: for comparison, several studies have included employee groups with limited nickel exposures or short-term employment. However, differences in personal habits, socioeconomic characteristics and other factors may limit the comparability between these groups. The generally applied procedure is to use the appropriate rates encountered in the general area, i.e., county, province or country. Again, this approach has its limitations, in this case mainly because the workforce studied is likely to represent a healthy sub-population capable of maintaining long-term employment. Thus, no ideal comparison group exists.

8) Significance of a non-positive study: Due to the limited availability of large human populations with long-term exposures to nickel, and due to the limitations discussed above, epidemiological studies are unlikely to produce an undisputable association between an exposure and a disease, unless the exposure is severe. Thus, the practical circumstances make it difficult to disprove the null hypothesis, i.e., that the exposure is

harmless. Such non-positive studies should not be taken as proof that no adverse effect occurs. A true, negative study would require that a large cohort with long-term exposure was followed over a long period, and that statistical calculations showed that an excess could have been reliably detected. For example, NIOSH has suggested that a 50% excess should be detectable (with 95% confidence) in a 30-year follow-up of individuals with at least 20 years of exposure. Thus, the epidemiological results are soft and must be interpreted prudently.

With the above considerations in mind, the epidemiological evidence accumulated will be reviewed. The text will first discuss the information regarding cancer rates in different processes of nickel production and nickel usage and then the data on particular cancers and the possible contribution of nickel exposure as a risk factor. Major parameters are given in Table 18 for the most recent cohort studies of nickel-production workers.

3.5.2 International Nickel Company, Ontario

Two studies of INCO employees have been published (Chovil et al., 1981; Roberts et al., 1984). The study by Chovil et al. (1981) examined the occurrence of lung cancer in a group of workers from the Copper Cliff sinter plant. The more recent study by Roberts et al. (1984) reported information on a more extensive follow-up of about 54,000 INCO employees.

On the basis of unpublished work by Sutherland, Chovil et al. (1981) identified a cohort of 495 men who had been employed at the Copper Cliff sinter plant for a period between 1948 and 1962 and who were alive by 1963. Total employment was five or more years with the company, including sinter plant service. The authors stated that, "it was not a complete roll of all the sinter plant workers but a somewhat stratified random selection that included all durations of exposure". Unfortunately, the selection process is not described. The Copper Cliff operation was extremely dusty and entailed burning of a mixture of impure nickel subsulfide with coke and a large recycle of partially oxidized "fines" on a travelling grate; ignition under a combustion hood was fuelled by oil until 1959 and subsequently by natural gas. The follow-up period was 1963-1977, 1978 for Ontario. However, 124 men (25%) could not be traced and were assumed to be alive. Cases of respiratory cancer were identified from the Workmen's Compensation Board of Ontario and from death certificates. Eight cases of sinus cancer were found, obviously a considerable excess although no expected numbers were given. A total of 54 cases of primary lung cancer occurred in the cohort,

37 being fatal within the study period, as compared to 4.25 expected deaths when using appropriate Ontario mortality rates. Interestingly, only three of the 54 lung cancer patients had entered employment after 1951. However, due to the questionable definition of the cohort and the insufficient follow-up, no exact information on cancer risks can be derived from this study. If the records are still available, a more detailed study would most probably be of considerable interest.

The extensive study by Roberts et al. (1984) dealt with INCO process staff who had worked at least 6 months with the company in Ontario and who were alive by January 1, 1950. However, sinter plant employees were included regardless of employment period, and unexposed office personnel was excluded. A total of 54,724 subjects were identified, of whom 50,436 had worked in Sudbury and 4,288 in Port Colborne. The length of employment was not specified in detail, but onset of exposure may in some cases have been as early as 1902 when INCO was founded. Occupational histories were available from company records, and about 1,000 job titles were used for exposure classification. Mortality was ascertained between January 1, 1950 and December 31, 1976 using company records and a record-linkage procedure. The validity of the latter method was assessed in a random sample of 1,000 subjects: as much as 15% of the mortality may have been missed. However, since record-linkage was responsible for locating only one-third of the deaths in this study, the total mortality is likely to be underestimated only by 5%. Men without any sinter plant experience showed a small excess mortality of questionable relevance, and respiratory cancer rates were not significantly elevated. However, sinter plant employees showed a significant excess in respiratory cancer mortality as determined from Copper Cliff and Coniston smelter records. The same is true for employees of the Port Colborne leaching, calcining and sintering department. The small numbers of larynx and kidney cancer cases would suggest that excess risk, if any, would be small. Lung cancer was seen in excess already 5-10 years after onset of exposure in Sudbury, while this was true only after about 20 years in Port Colborne. Nasal cancer began to appear after 15 years. A 15-year latency period used in the calculation of SMRs and statistical evaluations thus seems reasonable. Increased occurrence of lung cancer was apparent in men with only 2-5 months of exposure, and the risk seemed to increase with the duration of exposure. The SMR for lung cancer after 15 years increased by 89 per year of exposure at Copper Cliff and 21 at Port Colborne. The nasal cancer risk was apparently much higher at Port Colborne than at Copper Cliff, with two cases occurring in employees with less than 6 months of exposure. Due to the

small number of deaths observed, an estimate of 0.23 deaths due to nasal cancer per 1000 men per year of exposure must be interpreted cautiously. Only five deaths out of 43 due to lung cancer in Copper Cliff occurred in employees who worked for the first time in the sinter plant after 1951; this observation supports the conclusions of Chovil et al. (1981).

3.5.3 Falconbridge, Ontario

From company records, Shannon et al. (1984) identified 11,594 men who had been employed for at least 6 months and who had worked between January 1, 1950 and December 31, 1976. Some men started work before 1950, some as early as 1929 when the company opened its operations. Vital status as of December 31, 1976, was first assessed from the employment records. For the 6,370 men whose status could not be determined this way, the National Mortality Data Base was searched for possible deaths. In addition, independent follow-up was attempted through interviews, newsletters and other means. Vital status was determined from local information for 10.342 men (89.2%). Unless found in the National Mortality Data Base, the rest of the cohort was presumed alive. However, 36 who were stated to have died by other sources could not be found in the data base; these individuals were treated as alive in the study. Thus, the follow-up of this group was incomplete, and some deaths may have been overlooked. All deaths were accumulated in each department in which the individuals had worked. No case of nasal cancer was found, while 0.43 was expected for Ontario males. Lung cancer was in slight excess, with 46 cases observed against 37.5 expected. Five laryngeal cancers against 1.9 expected was not quite statistically significant. All cases of laryngeal cancer occurred more than 20 years from onset of exposure in particular in miners, though after variable lengths of exposure. With lung cancer a tendency toward more cases with longer employment in mines and smelter was seen. Four cases of prostate cancer occurred, against 1.8 expected. Mortality for all cancers and for cancer of the large intestine taken alone was significantly increased in men who had worked at the sinter plant. Due to the small numbers and the fact that many of the workers had not worked in just one department, a clear picture would be difficult to find. Also, some workers could have had exposures at other operations in the area, such as uranium mines and mills. However, only three of the men who developed lung cancer in this cohort had been employed for 1 month or more at the uranium operations. Also, diesel machinery was introduced in the nickel mines only in the mid-1960s. In conclusion, this study found no nasal cancers, and only a small excess number of lung cancers. Due to the limited power of the study and the insuffi-

cient follow-up, an increased risk of respiratory cancer, in particular in smelter workers, may well be present in this population.

3.5.4 Nickel refinery, Huntington, West Virginia

Copper-nickel matte from Sudbury was refined in Huntington, West Virginia, during 1922-1947, and a mortality study was performed of 1,855 men hired before 1947 and still on the payroll as of January 1, 1948 (Enterline and Marsh, 1982). This group included pensioners and active employees and was identified through personnel records. One-hundred-and-nine had worked for more than a year in the calcining department where crushed matte was oxidized at 1,200°C in gas-fired calciners. In addition, 157 had worked for a year or more in the nearby melting and casting department and, perhaps, some of the time at the calciners. This total group of 266 men were considered the refinery workers. Further, 137 men had worked at the refinery for less than a year, while 1,452 had never been employed at this part of the plant. Only 120 men were lost to follow-up, and only in two cases could a death certificate not be obtained from a deceased member of the cohort. In addition, a group of 1,354 workers employed during 1948-59 was studied for comparison purposes since they never had any exposure at the calciners. Expected numbers were calculated from national, state and local death rates. Two cases of sinonasal cancer were identified among refinery workers against 0.08 expected, while lung cancer was only marginally in excess. Among the nonrefinery workers, two probable cases of nasal cancers were discovered, although coded as bone cancer. From historical midget-impinger particle counts, estimates of gravimetric nickel levels were estimated to average about 5 mg/m^3 in the refinery, with lower levels elsewhere. When related to cumulated nickel exposure levels (during 20 years after onset), respiratory cancer in the groups examined and in the total cohort appeared to show some dose-relationship. However, the relative risk was rather low.

3.5.5 Nickel refinery, Kristiansand, Norway

A nickel refinery was established in Kristiansand, Norway, in 1910, originally based on local ores. After a temporary close-down, the facility was acquired by Falconbridge in 1929. Electrowinning of nickel takes place in electrodeposition cells of the Hybinette type. The production is now based on nickel-copper (Bessemer) matte received from Sudbury, Ontario. The refinery production was almost nil during 1940-45. Major improvements resulted in decreased exposure levels from the 1950s. The morta-

lity and cancer incidence have been examined by Pedersen et al. (1973) and followed up by Magnus et al. (1982). The first report dealt with 1,916 men who were alive by 1953, had been employed before 1961 and worked for at least 3 years (by 1979 the cohort size had increased to 2,247). The Norwegian Cancer Registry started in 1951 and is regarded as complete from 1953 and onwards. Classification into broad occupational groups depended on the job longest held during the employment; however, process workers who had spent longer time in non-exposed jobs were still classified as process workers. National rates were used for comparison. An increased rate of total cancer in roasting-smelting, electrolysis and other specified process workers was accounted for by a high number of respiratory cancers. During the period 1953-1979, 21 cases of nasal cancer had occurred, 8 of them among the roasting-smelting workers, with very high SMRs also in other occupational groups, including the electrolysis workers. Thus, five of the nasal cancers which had been diagnosed by 1971 were seen in workers involved with electrolysis for more than 15 years. Five cases of laryngeal cancer, already recorded by 1971 (and four of them in workers hired after 1945), was remarkable, with four of them occurring in the roasting-smelting group against 0.4 expected by 1971 and 0.6 expected by 1979. Eighty-two cases of lung cancer had occurred, against 22 cases expected by 1979. Data on smoking habits (never vs. ever smoked) were obtained from files of the medical officer of the plant, or from the next of kin. No interaction between nickel exposure and smoking could be detected, the two exposures resulting in an additive, rather than synergistic effect. While nasal cancer showed a peak in occurrence 25-34 years after first employment and a decreasing risk when first employment was more recent, lung cancer showed a shorter latency period and a smaller decrease, if any, with later time of first employment. This study is of particular interest because an excess cancer risk was seen in electrolysis department workers where easily soluble nickel sulfate may constitute the major part of the nickel exposures. However, the data published do not indicate whether or not the electrolysis workers had also worked in other process departments. Also, concomitant exposures to nickel subsulfide and oxides may have occurred in the electrolysis building, where leaching of the calcined matte took place.

3.5.6 Nickel refinery, Clydach, Wales

The Clydach nickel refinery was opened at Swansea, Wales, in 1902. Nickel matte was received from Sudbury, Ontario, and was refined by the nickel carbonyl (Mond) process. In the early years, a plane type of calciner was used for oxidation of the

matte, but a double-decker design was introduced by 1910, later improved in 1924, thus continuously decreasing the exposure levels. Copper was extracted from the matte by sulfuric acid which contained relatively large amounts of contaminant arsenic until about 1924. Further, cotton respirator pads were issued from 1922 and allegedly became popular. From 1934, the nickel matte received from Canada was changed: both copper and sulfur contents decreased to about 2% (Orford matte). More recently, additional improvements have resulted in lower exposure levels (Morgan, 1958). Several early reports showed an increased occurrence of respiratory cancer in Clydach workers, but only the most recently updated studies will be reviewed here.

A large cohort was first described by Doll et al. (1970). Paysheets were inspected for the first week of April of 1934, 1939, 1944 and 1949. All men recorded on any two paysheets were considered likely to having been employed for at least 5 years. Additional information, including first year of hire, for each worker was obtained from a register of new employees. A total of 845 men fulfilled the criteria. In a later report, paysheets for the first week of April of 1929 had also been examined, and the cohort now included 957 men; they had been exposed for various periods since 1902 (Doll et al., 1977). The size of this cohort should be compared to numbers given by Morgan (1958) of about 2,100 workers hired between 1902 and 1929, as many as 780 having worked for more than 20 years.

Thus, the cohort definition given by Doll et al. may have resulted in a selection which could potentially bias the results. Moreover, detailed information on the length of exposure in this group would in particular be prone to considerable bias. The cohort was most recently updated by Peto et al. (1984). Of the 945 men followed in this paper, only 18 were lost, and death certificates were obtained from all 788 men deceased between 1934 and 1981. A total of 78 nasal cancers was identified, but in three cases this diagnosis was not coded as the cause of death, and 19 occurred in men who left the refinery before 1934 and were therefore excluded. Two cases of nasopharyngeal cancer were possibly misclassified nasal cancers, but were not included in the calculations. All deaths due to nasal cancer occurred in men hired before 1925, but one case occurred in a man hired in 1928 where nasal cancer was given as a contributory cause of death. Similarly, the major excess in lung cancer occurred in men first hired before 1925, with a much smaller excess during 1925-29.

The largest cancer risk was associated with work at the calcining and Orford furnaces, a somewhat lower risk with work in the

copper sulfate and crushing departments. Risk was strongly related to the age at first employment for nasal cancer, but not for lung cancer. The latency period was 20-50 years for nasal cancer and somewhat shorter for lung cancer. Peto et al. (1984) speculated that nasal cancer risk may have decreased in the early 1920s due to improved hygiene, including cotton pads which would decrease exposure to large particles. Also, if the nickel compound acts as an initiator of carcinogenesis, this property would explain the increased risk at increasing age. With lung cancer, nickel would appear to act as a promotor of the cancer process. However, some of these findings could at least be partially explained by follow-up period starting from 1934 only. Thus, early deaths were not ascertained, and only the employees hired during the early years were followed for a sufficient period of time.

Cuckle et al. (1980) examined the mortality of Clydach refinery workers exposed to soluble nickel compounds in the wet treatment and chemical products departments. The two departments opened in 1937 and 1939, and employees with at least 12 months of exposure before 1961, a total of 197 men, constituted the cohort. Among these, 105 deaths had occurred, but 5 men were lost to follow-up. No nasal cancers occurred, but 13 cases of lung cancer were found, a significant excess above regional rates (expected number, 7.54), although non-significant when compared to rates for England and Wales. However, the occurrence of lung cancer was not related to the length of employment in the departments concerned or to the time from onset of exposure. The value of the information obtained is limited because of the small numbers involved.

3.5.7 Oxide ore refinery, Fort Saskatchewan, Alberta

Nickel oxide ore from the Sherritt Gordon mines in Oregon is refined by hydrometallurgical processes at the Fort Saskatchewan refinery, Alberta, where the operations started in 1954. Nickel exposures would mainly be in the form of oxide ore concentrate, nickel metal and some soluble compounds. A cohort of men employed for at least 12 consecutive months before the end of 1978 was followed until the end of 1978 using a computerized matching procedure in the Alberta Cancer Registry and the provincial registry for vital statistics (Egedahl and Rice, 1984). In addition, the cancer incidence encountered at the facility was registered during 1979-1982. However, cancer cases not reported or occurring outside Alberta would not be included. Of 720 nickel workers and 273 maintainance workers, follow-up was possible for 94%. Two cases of lung cancer were detected in the maintainance

group, otherwise no airway cancers were found. Two cases of renal cancer and two cases of Hodgkin's disease were seen, both more than three-fold in excess of expected numbers. However, none of the numbers showed any significant excess. With the short time interval since the opening of the plant and the small number of employees followed, this result is not surprising.

3.5.8 Oxide ore refinery, New Caledonia

Nickel oxide ore has been mined on the South Pacific Island of New Caledonia since 1866. Smelting has taken place since 1885 and now occurs in one large facility in the city of Noumea. Lessard et al. (1978) identified the cases of lung cancer which had occurred in the area during 1970-74 by using all available sources of information. A total of 92 new cases was identified, a rate similar to those seen in industrialized countries, but 3- to 7-fold in excess when compared to other Central and South Pacific countries. The exact current address was known for 42 cases, and a significant increase in lung cancer incidence was seen with decreasing distance to the refinery; this tendency was also seen in patients with previous employment at the facility. Information on smoking and employment at the refinery was obtained from 68 of 81 male patients, and they were then compared to 109 hospital controls. Age was controlled in the analysis. Nickel exposure was found to be an independent risk factor for lung cancer resulting in a relative risk of 3. Although this study was performed under difficult conditions, the deficiencies are minor and the results support the etiological role of nickel exposures in lung cancer.

3.5.9 Other nickel refineries

Several other studies have examined the cancer mortality in nickel production workers. They have not been reported in sufficient detail and apparently suffer from various deficiencies of study design. Although they therefore only contribute little new information, they are briefly mentioned below, as they in general tend to support the results obtained in the studies reviewed above.

Rockstroh (1958) examined the cancer incidence in German nickel refinery workers between 1928 and 1956. The refinery used a hydrometallurgical process, and arsenic contamination was probably widespread. A total of 45 cases of lung cancer was found in the exposed workers, as contrasted to only one in office personnel. However, the calculations were based on average numbers of refinery workers per year, and the size of the comparison group was not indicated. Despite this problem and the possible

lack of standardization as to age, the excess occurrence of lung cancer in the refinery workers is surprisingly large.

Saknyn (1970; 1973) studied the mortality in nickel refinery workers from a total of five facilities in the Soviet Union and compared it to the local cancer rates. The actual numbers were not given, but lung cancer in refinery workers was between 2.8- and 3.8-fold higher than expected.

Tsuchiya (1965) conducted a survey of lung cancer incidence in the three-year period 1957-1959 in a random sample of 200 industries in Japan employing more than 1000 workers each. When compared to the national average, the handling of nickel (19 cases) and chromium (22 cases) was associated with a significant, two-fold risk, which however became insignificant when nickel and chromium were treated separately. This study only dealt with active employees with varying lengths of exposure and may have suffered from ascertainment bias.

Olejar et al. (1982) studied the cancer incidence in workers from a Czeckoslovakian facility where an oxide ore has been refined for nickel since 1963. During 1971-1980, 27 malignant tumours were diagnosed at a local polyclinic, including 8 lung cancers. This number was only slightly above the expected number, and all workers had smoked more than 25 cigarettes per day. However, with the short latency period since 1963, the result is not surprising, and subsequent follow-up should be awaited.

3.5.10 Nickel-using industries

Exposure to nickel dust occurred at the Oak Ridge Gaseous Diffusion Plant in Tennessee, USA, during the production of barrier material for isotopic enrichment of uranium. The fine nickel powder may, to some degree, have been oxidized. The median for nickel exposure measurements during 1948-1963 was 0.1 mg/m^3, but extremely high levels occurred on occasion (Godbold and Tompkins, 1979). A cohort of 814 barrier workers had worked at the plant at least one day during 1948-1953, but the total length of employment at the barrier plant varied between three days and 25 years, with a median of 3.8 years (Cragle et al., 1984). A comparison group consisted of 7,552 men employed for at least one day by the company but not exposed to nickel. Vital status by 1977 was obtained for 90% of the nickel-exposed workers and 93% of the controls, and 97% of death certificates were obtained. No excess mortality was seen, and cancer of the respiratory system showed a number which was lower than expected. However, three cases of cancer of the buccal cavity and pharynx represented an almost

three-fold excess compared to U.S. rates and a ten-fold excess when compared to the control group. Although misclassification cannot be ruled out, this observation would deserve attention.

Several other studies have dealt with exposure to metallic nickel or nickel oxide dust, such as die-casting and electroplating (Silverstein et al., 1981), metal polishing and plating (Blair, 1980), the production of high nickel alloy (Redmond, 1984), stainless steel (Cornell, 1984), nickel alloys (Cox et al., 1981) and nickel-chromium alloys (Cornell and Landis, 1984). These studies vary with regard to epidemiological design, size of cohort, length of follow-up period and significance of exposures other than nickel. Few exposure data are given, although the nickel alloy workers followed by Cox et al. (1981) were probably exposed to average nickel levels of 0.5-0.9 mg/m^3. These studies did not identify any risk of nasal cancer in these occupations. Excess numbers of lung and other cancers were inconsistent and may not necessarily be attributed to nickel exposures.

Welders may be exposed to nickel oxide, especially when welding on nickel alloys (Polednak, 1981) or stainless steel (Sjogren, 1980). Interpretation of studies in this area is hampered by the simultaneous exposure of welders to chromates and, perhaps, other carcinogens. On the basis of several epidemiological studies showing an increased risk of respiratory cancer in welders, Langård and Stern (1984) concluded that such risk, especially in high-alloy and stainless steel welders, could be related to the presence of chromium and nickel in the welding fumes. This possibility is currently being investigated.

Likewise, cohorts of nickel-cadmium battery workers have been examined for possible excess cancer mortality (Sorahan and Waterhouse, 1983; Andersson et al., 1984). Again, the results obtained concur very little with the experience from the nickel-producing industry, and possible excess mortality may well be caused by exposures other than nickel.

3.5.11 Case reports and case-referent studies

From detailed case studies, the development of nasal cancer appears to begin with dryness and crusting of the mucosa of the middle turbinate and the hiatus semilunaris; squamous metaplasia then progresses to atypia and dysplasia, intra-epithelial carcinoma and invasive cancer (Barton and Hogetveit, 1980). The poorly differentiated tumours tend to be aggressive locally, metastasize widely and carry a poor prognosis when seen late in the disease (Andrews, 1983).

As nasal cancer is a rare disease in the general population, the case-referent (or case-control) design has been used to elucidate the possible etiology. Such studies depend heavily on accurate occupational histories and detailed information on exposures decades ago (see section 3.5.1). In a British study (Acheson et al., 1981), an excess risk for nasal cancer was found in furnace and foundry workers, only partly due to several cases in employees from the Clydach nickel refinery. Among nasal cancer cases in Connecticut, no relation could be found to several metal-related occupations where nickel exposures were likely to occur (Roush et al., 1980). In a small Finnish study, no relation to occupational nickel esposure was found (Tola et al., 1980). However, in a joint Finnish-Swedish-Danish study which used detailed questionnaires on occupational and other factors, an excess risk was related to nickel exposure in welding, flame-cutting and soldering; a minor excess was seen in relation to electroplating (Hernberg et al., 1983). Most interestingly, only one of the nickel-exposed cases had been involved with the production of nickel; most of the nickel exposure occurred in the user industries where chromium and cutting-oils may also have occurred. Thus, nickel-related nasal cancer may possibly be a risk outside the nickel-producing industries.

Cancer of the larynx has occacionally been seen in increased numbers in cohorts exposed to nickel, as discussed above. A case-referent study of 204 laryngeal cancer patients and a referent group in southern Ontario showed no relation to occupational exposure to nickel, while tobacco, alcohol and asbestos were major risk factors (Burch et al., 1981). However, a Danish study found a small excess risk related to potential nickel exposure from alloys, battery chemicals and chemicals used in the production of plastics (Olsen and Sabroe, 1984). Although the evidence is limited, nickel would seem unlikely to constitute a major risk factor for laryngeal cancer.

Lung cancer is the most frequent cancer type in nickel-producing workers. Most patients are smokers, in particular those with anaplastic carcinoma or epidermoid carcinoma (Kreyberg, 1978). A small case-referent study of lung cancer cases at an aircraft engine factory showed no relationship to nickel exposures (Bernacki et al., 1978). Some studies suggest that occupational nickel exposure in the metal trades may be a risk factor for lung cancer (Bergmann, 1982; Pastorino et al., 1984), but the results are difficult to evaluate because of the overwhelming influence of tobacco and asbestos. However, a large Canadian study showed a statistically significant odds ratio of 3.1 for the nickel-lung

association with an indication of a dose-response relationship (Gerin et al., 1984). Thus, although many risk factors contribute to the high risk of lung cancer in males, occupational nickel exposure could well be an important contributory factor.

3.5.12 Conclusions

The carcinogenic effects of nickel occur with a considerable latency time after the initiation of exposure. Thus, the health effects found in epidemiological studies now are the result of exposures decades ago. This is a problem of major significance, as the magnitude and exact speciation of past exposures is difficult to evaluate. Several studies have been carried out at nickel smelters and refineries. Although each of them suffers from some deficiencies, as are normal in such retrospective studies, the findings in concert strongly indicate that nickel from the calcining and sintering operations is a potent carcinogen resulting in nasal and pulmonary cancers. Some risk appears to be present in other operations, such as Orford furnace, copper sulfate and crushing departments, and one study has suggested a risk associated with soluble nickel compounds in the electrolysis department, although this finding has not been confirmed. Only one study demonstrated an exposure-response relationship which, however, was not statistically significant. In other studies, a relationship between increased exposure time and cancer risk could be demonstrated. In nickel-using industries, no excess cancer related to nickel exposures has been demonstrated beyond doubt; in many cases, concurrent exposures to other potential carcinogens constitute a confounding variable which makes it difficult to interpret the findings. However, the studies have not excluded that the cancer hazard is restricted to the nickel-producing facilities only. Further, case-referent studies of respiratory cancers suggest that a nickel-related etiology may well exist in the nickel-using industries.

4. EFFECTS ON THE IMMUNE SYSTEM

The immune system has important defensive functions against both organic and inorganic materials, elimination of invading microorganisms and elimination of foreign cells, e.g., mutated cells and cancer cells (Roitt, 1980). The cellular immune system consists of the thymus, the bone marrow, different kinds of peripheral lymphatic tissue and circulating cells, including macrophages, lymphocytes and natural killer cells.

The immune system functions by the following mechanisms:
- phagocytosis by macrophages and other cells
- "neutralization" of antigenes by antibodies produced by B-lymphocytes or by mediators released by T-lymphocytes.
- destruction of foreign cells by natural killer cells
- destruction of foreign cells by activation of the complement system.

These mechanisms often function synergistically and have a regulatory influence on each other. An interaction with any of the components or mechanisms involved in the immune system might well have an inhibiting effect on other aspects of the immune system.

Allergy is frequently regarded a disadvantageous reaction of the immune system, and a teleological explanation for the development of, say, allergic contact dermatitis or asthma, has not been found. Operationally, four different allergic reaction types may be determined. Type IV is the T-lymphocyte mediated reaction involved in contact dermatitis. In immediate asthma, rhinitis, and urticaria (type I), the allergic response is due to the production of specific antibodies by B-lymphocytes. A delayed form (type III) could conceivably be involved in some cases of asthma. However, the type of reaction may not always be easily recognized in clinical cases.

4.1 Nickel-associated contact dermatitis

In the pathogenesis of allergic contact dermatitis, several steps may be recognized (Adams, 1983). An individual in the refractory stage may get sensitized to the allergen during the inductive phase, which normally takes 2-3 weeks but may be as short as 4 d. Reexposure of fully sensitized skin to even minute quantities of the allergen will elicit or provoke an eczematous response which begins within 12 h and is fully developed at 48-72 h after which it subsides. After the eliciting phase, the sensitivity will remain, usually for years and frequently for a lifetime, or it may gradually decline over an extended period if no further

reaction takes place.

Nickel is a hapten which must react with a protein, most likely albumin (see section 4.2), in order to induce an allergic response. Sensitization is only known to occur after nickel absorption through the skin, whereas provocation possibly can happen even after ingestion of nickel with food (Menne and Hjorth, 1982; Nielsen and Flyvholm, 1984). Nickel allergy may cause subsequent development of chronic hand eczema with recurring, itching eruptions and deep vesicles with some or no erythema localized on the palms, volar aspects and sides of fingers (Menne and Hjorth, 1982). Exacerbations may occur at weekly or monthly intervals and can result in disability, especially if the person with nickel allergy is working in an occupation with exposure to moisture and aqueous solutions, even with minute nickel concentrations.

Nickel allergy can be demonstrated either by patch testing with 5% nickel sulfate or by questionnaire/interview relating to symptomatic nickel-associated contact dermatitis (especially earlobe dermatitis). Neither method may be 100% reliable. Kieffer (1979) found negative patch-test reactions among 13 out of 28 patients (46%) who indicated symptoms of nickel allergy. Similarly, positive patch-test reactions were found among 8 out of 387 persons (2%) without any nickel-related symptoms.

Patch testing was used in an investigation performed by Prystowsky et al. (1979) in San Fransisco: the prevalence in 1158 paid volunteers was 9% among women and 0.9% among men. This investigation may suffer from some selection bias, as the population studied was not necessarily representative of the general population. Finnish and Danish investigations using patch testing of other non-representative populations showed average prevalences of 8-9.5% among women and 0.8-2.8% among men (Kieffer, 1979; Menne, 1978; Peltonen, 1979).

Menne et al. (1982) used an interview technique to examine the prevalence of nickel allergy and hand eczema in the Danish female population. The sample included 2,552 women and was representative of the general population regarding age, geographical distribution and occupation. Among the 1,976 participating women the prevalence of nickel allergy was found to be 14.5% in the total sample and 18.9% among the 40-49 year old women; 57% of the nickel-allergic women had experienced hand eczema. This finding is in agreement with other studies by Christensen and Moller (1975), Menne (1978) and Peltonen (1979) who found prevalences of hand eczema among persons with nickel allergy ranging from 40 to

52%. Furthermore, Menne et al. (1982) found that nickel allergy most often developed during the teenage years and that the annual incidence in this age group increased from 0,7% around 1950 to 1,5% in recent years.

Sensitization of such a large fraction of the population is a result of daily skin contact with corrosive metal objects containing nickel. Such everyday objects include jewelry made of German silver (containing 10-20% nickel), nickel-plated spectacle frames, buttons, clasps, buckles, zippers, etc. (Fisher, 1973).

As indicated in section 1.5, dermal exposure is frequent in several occupations. In particular, moist or wet conditions tend to weaken the skin barrier and also provide an easier passage of soluble nickel ions into and through the stratum corneum. Further, preexisting irritant dermatitis, pressure, friction and sweating constitute predisposing factors. Although many patients with an occupational nickel-related contact dermatitis may have been sensitized elsewhere, working conditions frequently provoke the outbreak of eczema.

Genetic factors may also play a role, as indicated by a high concordance rate in monozygotic twins (Menne and Holm, 1983). However, nickel allergy and nickel-associated contact dermatitis only develops as a result of nickel exposure, although the dose necessary may vary. No test is available to identify individuals who would be particularly likely to become sensitized.

During the period 1966-1980, only 83 claims were allowed by the Ontario Workmens' Compensation Board for contact dermatitis due to nickel, an average of 5-6 cases per year (Acres, 1982). However, these claims were related to a few specific nickel-exposed trades only, and other cases of nickel-induced contact eczema may be found in the large number of other eczema claims allowed. The above number appears to be very low, as compared to an annual average of about 100 recognized cases of occupational contact dermatitis due to nickel in Denmark, a country with 5 million inhabitants (Menne and Bachmann, 1979b). Thus, occupational nickel-related contact dermatitis may well be an overlooked or insufficiently reported disease in Ontario.

4.2 Nickel-provoked respiratory allergy

Asthma has been reported in several patients in relation to respiratory exposure to soluble nickel compounds (McConnell et al., 1973; Malo et al., 1982; Block and Yeung, 1982; Norvey et al., 1983; Malo et al., 1985; Cirla et al., 1985; Davies, 1986).

Different patterns of asthmatic responses may be seen (Parkes, 1982). The immediate-type asthma develops within minutes of exposure or bronchial provocation tests, reaches a maximum in 10-20 min and subsides within about 2 h. The late (or non-immediate) form usually starts up to several hours after exposure, reaches a maximal response in 4-8 h and fades away in 24 h. Further, a dual form includes both immediate and late asthmatic reactions.

All forms have been described as a result of occupational nickel exposures. Thus, immediate (Block and Yeung, 1982; Malo et al., 1982), late (McConnell et al., 1973; Malo et al., 1985) and dual-type asthma (Novey et al., 1983) have been documented.

In some cases, the asthmatic reaction to nickel salts was associated with contact dermatitis (McConnell et al., 1973; Block and Yeung, 1982; Cirla et al., 1985), but negative patch test results for nickel (Mitchell, 1981; Cirla et al., 1985) do not support any association between the two allergic diseases, except that they may both be caused by occupational exposure to soluble nickel compounds.

More importantly, asthma may be associated with urticarial rashes, although perhaps at different points in time (Kaplan and Zeligman, 1963; Malo et al., 1982). Also, nickel inhalation may cause rhinitis, yet another type-I reaction (Niordson, 1981).

In the diagnosis of asthma, bronchial provocation tests are usually necessary to identify the cause (Parkes, 1982). Prick tests are used to document a type-I reaction, but a negative reaction may be encountered although a provocation test with nickel is positive (Malo et al., 1985). In such cases, a non-specific bronchial reactivity may be involved.

Further examination of the immunological mechanisms involved has utilized serological techniques in patients with nickel-associated asthma. Total IgE may not be increased in the patients (Malo et al., 1982; Novey et al., 1983). Specific IgE antibodies against nickel or albumin-bound nickel may be determined by a radio-allergosorbent test (RAST) and has shown increased levels in patients (Malo et al., 1982; Novey et al., 1983), although this result may only indicate that nickel exposure has taken place. More detailed studies by Dolovich et al. (1984) and Nieboer et al. (1984) strongly indicate that, at least in the patient studied, the binding of nickel to the primary copper-binding site of albumin changes the structural features of the molecule and renders it potentially allergenic.

Nickel-provoked asthma has most frequently been described in relation to nickel plating (McConnell et al., 1973; Malo et al., 1982; Novey et al., 1983; Cirla et al., (1985), but metal polishing (Block and Yeung, 1982) and production of nickel salts for catalysts (Davies, 1986) have also been recorded as cause of nickel-exposure. Asthma occasionally occurs as a result of inhalation of welding fumes (Keskinen et al., 1980; Bjornerem et al., 1983) and may be caused by nickel, although other factors could also be involved.

The prevalence of nickel-related asthma is most likely underestimated due to several factors. Delayed responses may not suggest an obvious occupational causation. Exposures at work are often complex, and nickel may not necessarily be suspected as a cause. The verification of the etiological diagnosis by bronchial provocation, skin reaction and serological tests is cumbersome and may not be carried out, unless a positive result is strongly suspected likely. Finally, the heterogeneous character of the cases described, including one with a negative prick test, suggests that nickel-associated asthma is not a well-defined clinical entity and that several types may occur.

In addition to the clinical pictures described above, nickel may also cause other forms of respiratory disease by immunological mechanisms. First of all, freshly formed nickel oxides (e.g., from founding or welding) may cause metal fume fever (Parkes, 1982). Further, nickel exposure has been related to Loffler's syndrome (Sunderman and Sunderman, 1961). The long-term effects of respiratory exposure to nickel, including the possible development of pneumoconiosis, are poorly known.

4.3 Immunotoxic effects

Immunotoxic effects may be exerted by cytotoxic actions on immune cells or by causing alterations of the physiology or suface markers of the cells. Such changes could result in an inhibition of immune function or in the potentiation of immune responses due to autoimmunity (allergy is dealt with in sections 4.1 and 4.2).

Koller (1980) has reviewed the literature concerning the immunotoxicology of heavy metals, including nickel, and emphasized that nickel enhances infectiousness of EMC virus and *Streptococcus pyogenes* in mice. Furthermore, nickel may depress titers of circulating antibodies to T-phages, inhibit the interferon response and inhibit the phagocytotic ability and other properties of macrophages. More recent investigations are reviewed below.

Bencko et al. (1983) found increased average values of serum immunoglobulins IgG, IgA and IgM in 38 workers occupationally exposed to nickel when compared to the values obtained from a non-exposed control group. Furthermore, they found increased levels of the following serum proteins: alpha$_2$-macroglobulin, alpha$_1$-antitrypsin, coeruloplasmin and lysozyme. Such elevations in serum proteins can be due either to nickel-enhanced stimulation of protein synthesis or to overcompensation of nickel-induced inhibition of protein synthesis.

Spiegelberg, et al. (1984) studied the effect of inhaled NiO particles on alveolar macrophages and the humoral immune system of male Wistar rats continuously exposed to nickel oxide aerosols for 4 weeks and 4 months, respectively. The number of alveolar macrophages remained at the same level as the controls after exposures to 50 and 100 ug Ni/m^3 and decreased significantly at 400 and 800 ug Ni/m^3 exposures were given for 4 weeks. Exposure to 800 ug Ni/m^3 caused a high fraction of killed macrophages as well. The morphology of the alveolar macrophages was altered as the size of macrophages increased after exposure to 100 ug Ni/m^3 and the number of macrophages with more than one nucleus increased at exposure to 400 ug Ni/m^3. Moreover, after exposure to 400 ug Ni/m^3, the phagocytic activity was enhanced to 141% of that found in controls; however, at 800 ug Ni/m^3 the phagocytic activity was decreased and accompanied by a loss of morphological integrity of the cells. In other words, a general stimulation of the alveolar macrophages was observed with increasing levels of exposure up to a certain point where the nickel oxide had a toxic effect on the cells. After 4 months of exposure, the same pattern was seen but at lower concentrations. Thus, at 25 ug Ni/m^3, the number of macrophages was increased, but it was slightly decreased after exposure to 150 ug Ni/m^3. The size and number of macrophages with more than one nucleus increased at 25 and 150 ug Ni/m^3. The humoral immune response to injected sheep erythrocytes showed a decrease that was related to the nickel oxide exposure level. The antibody production in spleen cells was suppressed after exposure for 4 weeks to 200 ug Ni/m^3 and for 4 months to 150 ug Ni/m^3. The effect was more pronounced in the spleen than in serum.

Rae (1983) exposed human polymorphonuclear leucocytes (PMN) *in vitro* to subtoxic nickel concentrations. The ability of PMN to phagocytize and kill *Staphylococcus epidermis* was reduced by about 50% during an 18 h exposure to a nickel concentration of 0.05 umol/l (3 ug/l).

Smialowicz et al. (1984) investigated the effects of nickel chloride ($NiCl_2$) on the cellular and humoral immune responses of mice after intramuscular injection of doses of 9.1, 18.3 and 36.6 mg $NiCl_2$/kg (2.3, 4.5 and 9 mg Ni/kg) of body weight. Immune-function tests included assays for lymphocyte and macrophage function. They found that a single i.m. injection of 18.3 mg $NiCl_2$/kg caused an involution of the thymus within 2 days following treatment. A decrease in the percentage of T-lymphocytes was observed in the spleens of treated mice, but no change in number of B-lymphocytes was observed. The in vitro response of lymphocytes to the T-cell mitogens phytohemagglutinin and concanavalin A and to the combined B- and T-cell mitogen pokeweed mitogen, was reduced in nickel-treated mice, but not the response to the B-cell mitogen lipopolysaccharide. Further, the primary antibody response to a T-cell-dependent antigen (sheep erythrocytes) was also suppressed. Macrophage function as measured by detoxification of endotoxin and phagocytotic activity was not significantly changed. In contrast, natural killer cells (NK-cells) showed suppressed activity. These results indicate that nickel chloride ($NiCl_2$) predominantly affects T-cell mediated immune responses and natural killer cell activity.

NK-cells have received increased attention in recent years because of their potential role as primary cytotoxic effector cells against tumours. An additional study by Smialowicz et al. (1985) confirmed the suppression of NK-cell activity. Intramuscular injection of 18.3 mg/kg of $NiCl_2$ (4.5 mg Ni/kg) either as a single injection or administered over a 2-week period caused a reduction in NK-cell activity of splenocytes from CBA/J and C57BL/6J mice. This dose of nickel chloride also decreased the clearance of tumour cells from the lungs of $NiCl_2$-treated mice and enhanced the development of B16-F10 lung tumour colonies. The reduction in NK-cell activity was neither associated with a reduction in the total number of spleen cells nor with increased numbers of suppressor cells.

While nickel suppresses NK-cell activity, manganese in the form of $MnCl_2$ seems to enhance it, as studied by Smialowicz (1985). Manganese, injected i.m. into mice in doses of 40 or 80 mg/kg of Mn as $MnCl_2$, significantly enhanced NK-cell activity. When nickel and manganese were injected concomitantly into contralateral thighs, the suppression of NK activity by $NiCl_2$ was preempted by $MnCl_2$. Injection of $MnCl_2$ 1 day prior to, but not 1 day after $NiCl_2$ administration also resulted in enhanced NK-cell activity. These results may provide some insight into the inhibitory effect of manganese on nickel-induced carcinogenicity in rats dealt with in the sections 3.4.5 and 3.4.6.

Enhanced NK-cell activity and cytotoxic function of T-lymphocytes might be mediated by interferon, and the effect of nickel on interferon production is therefore of particular interest.

For example, Pribyl and Treagan (1977) showed that pretreatment of cell cultures with nickel severely inhibited interferon production. Sonnenfeld et al. (1983) exposed mouse embryo fibroblast cultures to various concentrations of amorphous or crystalline nickel sulfide (NiS). The latter inhibited the production of interferon at non-cytotoxic concentrations, i.e., 1 ug/ml (0.6 ug Ni/ml) while amorphous NiS had no effect on interferon production at 10 ug/ml (6.5 ug Ni/ml). The effects of crystalline NiS on interferone induction could be related to its carcinogenic effects but may also be a mere reflection of the phagocytosis of crystalline NiS.

Fishelson and Muller-Eberhard (1982) and Fishelson et al. (1983) studied the effect of nickel ions on the complement system. The complement system is a well-balanced system of circulating inactive components which functions by triggering an enzyme cascade system finally leading to membrane lesion and cell lysis. This enzyme cascade can be triggered by formation of two enzymes C3b,Bb and C4b,2a, both of which require magnesium to be formed. The studies demonstrated that nickel can replace magnesium and that nickel has a higher affinity to the enzymes, thus resulting in a longer half-life of the enzymes in the order of 2 - 10 times the half-life of the enzymes formed with Mg. This event may well upset the otherwise well-balanced complement system and lead to a weakened defense against potentially pathogenic foreign cells.

The immune system has important functions in the defense against foreign cells, including cancer cells. Immunotoxic effects could potentially be involved as a factor related to the increased occurrence of respiratory cancers in certain nickel-exposed occupations (see section 3.4). In this regard, one may speculate that workers who remain in nickel-related jobs would be unlikely to include those who have a very reactive immune system which causes allergic responses. Thus, self-selection among nickel-exposed workers and immunotoxicity could conceivably result in an increased susceptibility to the development of cancer.

4.4 Conclusions

Nickel may have profound effects on the immune system. First of all, nickel is a common skin allergen, in recent studies the most frequent cause of allergic contact dermatitis in women and one of the most common causes in men. The sensitization appears to occur

mainly in the young age groups, usually caused by non-occupational skin exposures. However, subsequent provocation of hand eczema may be caused by occupational exposures, especially to nickel-containing fluids and solutions. In some cases, the hand eczema may cause incapacitation. In addition, several cases of nickel-associated asthma have been described, and this disease may not be as rare as indicated by the few case reports. Further, nickel has been shown in experimental studies to cause immunotoxic effects, in particular increased infectiousness, decreased natural killer cell activity, inhibition of interferon production and interference with functions of the complement system. Although some of these effects have been demonstrated at concentrations likely to occur under occupational exposure conditions, the health significance of these findings is difficult to evaluate. However, immunotoxic effects could contribute to the development of cancer.

5.REPRODUCTIVE EFFECTS

The biological functions which form the basis for reproduction and organogenesis are varied in nature and in their susceptibility to adverse effects of chemical compounds, such as nickel and its compounds. In theory, toxic effects on the reproductive system can be produced at several levels. Toxicity to the sexual or endocrine organs may lead to a decrease in fertility. Due to the capability of nickel to pass the placental barrier (section 2.8), a toxic effect can be exerted during the organogenesis period lasting from the 20th to the 60th day of human pregnancy. A toxic effect on the embryo during this stage can result either in the death of the embryo (abortion) or major morphologic abnormalities. Later in the foetal period, a toxic effect will result in physiologic defects and minor morphologic abnormalities. A possible effect of nickel on uterine contraction may be related to a potential competition with calcium (see section 6.3). Unfortunately, no human data related to nickel exposures are available, only experimental studies are reviewed below.

5.1 Influence on fertility

The influence of nickel on male germ cells was studied by Jacquet and Mayence (1982) by treating two groups of male mice with 40 and 56 mg of nickel nitrate, respectively (corresponding to 8 and 12 mg of nickel). After this treatment, the males were every week mated with superovulated females for 5 consecutive weeks. The number of fertilized females and the number of cleaved eggs were counted and the development of embryos to blastocysts and implantation was determined. They found that a dose of 12 mg of Ni significantly reduced the fertilization rate 3 and 4 weeks after treatment but did not affect development of embryos. Thus, high levels of nickel can result in a toxic effect on spermatids and spermatogonia.

5.2 Embryotoxicity and teratogenicity

The embryotoxic and teratogenic potentials of nickel have been thoroughly reviewed by Leonard et al. (1981), Sunderman et al. (1983b), Leonard et al. (1984) and Leonard and Jacquet (1984). A successful pregnancy requires integration of the hypothalamic, pituitary, ovarian and uterine functions and depends also on the mother's effectiveness in shielding the intrauterine occupant from environmental agents. At all stages, maternal factors, such as hormonal equibrilium and placental function, play a role. Thus, embryotoxic and teratogenic effects may result from direct insult to the embryo, indirectly through effects on the mother,

or from combinations of the two.

To examine the indirect effects exerted through the mother, La Bella et al. (1973a; 1973b) studied the release of prolactin from the rat pituitary, in vivo and in vitro. They found that nickel ions had an inhibiting effect, which could possibly affect the fine interactions between the hypothalamus and the pituitary gland needed to maintain pregnancy.

Sunderman et al. (1978b) administered $^{63}NiCl_2$ (12 mg of Ni/kg, i.m.) to a group of nonpregnant female rats and to groups of pregnant rats on day 8 or 18 of gestation. After 24 h they found much higher (7 to 8 times greater) pituitary concentrations of ^{63}Ni in pregnant rats than in nonpregnant rats. Parallel experiments with similar administration (16 mg of Ni/kg, i.m.) to a group of rats on day 8 of gestation reduced the mean number of live pups per dam and resulted in diminished body weights of fetuses on day 20 of gestation and of weanlings at 4 to 8 weeks after birth. These observations led Sunderman et al. (1978b) to speculate that the effects observed may be mediated by nickel-induced maternal hormonal imbalance, rather than by a direct toxic effect of nickel ions on the products of conception.

Studies of embryotoxicity and teratogenicity of nickel compounds are listed in table 19. Phatak and Patwordhan (1950) administered nickel carbonate in the food to rats throughout gestation. At doses of about 0.5 and 1 g Ni/kg of food, an increased nickel content of the pups was observed, but no toxic effect with regard to litter size or body weight. Ridgway and Karnofsky (1952) studied the toxic effect of nickel chloride on chick eggs. They found an LD_{50} on 0.05 mg Ni/egg when nickel was administered on day 4 of gestation.

Schroeder and Mitchener (1971) administered nickel (5 ppm) in drinking water to three consecutive generations of rats. An increased number of neonatal deaths and runts was observed in all three generations as well as a decreased male/female ratio in the third generation.

Ferm (1972) found that intravenous administration of nickel acetate in doses of 2-30 mg/kg of body weight (0.5-7 mg Ni/kg) to hamsters on day 8 of gestation caused embryotoxic effects, in particular resorption and mortality of embryos. A few general malformations were seen in surviving embryos.

Analogous to the study by Schroeder and Mitchener (1971), Ambrose et al. (1976) performed a three-generation reproductive study in

rats, using a larger number of animals and higher doses of, 250, 500 and 1000 mg Ni/kg of food. In the first generation, a higher incidence of stillborn pups was seen at all dietary levels of nickel, and decreased body weights of weanlings in all generations at 1000 mg Ni/kg of food. These three-generation studies with a continuous exposure to nickel do not allow a distinction between the various parts of the gestation which may be influenced by nickel. On the other hand, the situation is more similar to the daily exposure of humans, and the possibility of missing a sensitive period of the gestational development is minimized.

Sunderman et al. (1978b) studied the embryotoxicity and foetal toxicity of soluble nickel chloride and sparingly soluble nickel subsulfide given by i.m. injection to rat dams. They found that $NiCl_2$ resulted in reduction of the number of live pups when given in one injection on day 8 of gestation in doses of 12 and 16 mg Ni/kg of body weight and when given in 10 injections of 2 mg Ni/kg on days 6 to 10. At the higher concentration, i.e., 16 mg Ni/kg, lower body weights of the foetus and of pups 4, 6 and 8 weeks after delivery were observed. $NiCl_2$ administered to pregnant rats on day 18 of gestation for studying the foetotoxic effect showed no foetal mortality, except at high doses which caused 50% mortality of mothers within 24 h. When Ni_3S_2 was injected i.m. on day 6 of gestation, a reduction in the number of live pups was seen at the dose level of 80 mg Ni/kg. In this study no evidence of teratogenicity of nickel was obtained.

Lu et al. (1979) administered 1.2 - 6.9 mg/kg of nickel as $NiCl_2$ intraperitoneal doses to groups of mice on days 7 to 11 of gestation. The sublethal doses of 4.6 mg/kg or more (about one tenth of LD_{50} of pregnant mice) resulted in significant embryotoxic effects in terms of increased resorption rates and decreased foetal weight in agreement with other investigators. Further, they found a delay in skeletal ossification and a high incidence of malformation, effects that had been observed earlier only by Ferm (1972). The following malformations were observed to occur at in increased incidence: anencephaly, cerebral hernia, open eyelid, cleft palate, micromelia, ankylosis of the extremity, club foot and skeletal anomalies, such as vertebral and/or rib fusions (cerebral, ocular, palatine, and skeletal anomalies). The highest malformation incidence was observed when nickel was injected on day 8 or 9 of gestation.

Subsequently, Gilani and Marano (1980) observed the following malformations in chick embryos following injection of nickel chloride: anencephaly, everted viscera, short and twisted limbs,

microphthalmia, haemorrhage and reduced body size.

Weischer et al. (1980) exposed rats by inhalation to nickel oxide (NiO) aerosols in concentrations equal to 0.6, 1.3 and 2.5 mg Ni/m^3 throughout the gestation period. The body weight of the foetus was reduced at the two highest exposure levels, whereas the number of foetuses did not differ from the number of foetuses seen in control animals.

Storeng and Jonsen (1980) used preimplantation mouse embryos to investigate the toxic effect of nickel chloride on early embryo development *in vitro*. A nickel concentration of 0.6 mg/l as nickel chloride inhibited the normal development of 2-cell embryos (day 2), whereas 18 mg Ni/l was needed to inhibit the development of 8-cell embryos (day 3). Subsequently Storeng and Jonsen (1984) found that the effect of $NiCl_2$ on the development of day 3 mouse embryos *in vitro* was reversible after a short exposure period. Also, intraperitoneal injections of nickel chloride in the first days of gestation resulted in a larger frequency of both early and late resorptions and a larger frequency of stillborn and abnormal fetuses (Storeng and Jonsen, 1981). This finding indicates that nickel may influence mouse embryos during the passage through the oviduct with subsequent effect on the development after implantation.

As already discussed in section 3.4.5, Sunderman et al. (1981) studied, transplacental carcinogenicity of nickel subsulfide by i.m. injection of 20 mg of Ni_3S_2 (15 mg Ni) to 8 pregnant rats on day 6 of gestation. They observed the progeny of the animals for 26 months and found no effect upon tumour incidence. However, reduced body weights of progeny at the age of 6, 12 and 18 months were seen in agreement with earlier observations.

In relation to the studies on erythrocytosis (in section 6.2), Sunderman et al. (1983b) examined whether or not intrarenal injection of Ni_3S_2 in female rats prior to breeding would stimulate erythrocytosis in the progeny. Ni_3S_2 was administered to the dams 7 days before mating. Haematocrit values indicated that erythrocytosis developed in the Ni_3S_2-treated dams, but not in their offspring, suggesting that increased maternal erythropoietin production does not stimulate erythropoiesis in the foetus. The body weight of pups from Ni_3S_2-treated dams was again significantly lower at 2 and 4 weeks postpartum compared to weights of control pups.

Most recently, Mas et al. (1985) studied the acute toxicity and teratogenicity of nickel given as $NiCl_2$ to pregnant mice. The

susceptibility of the pregnant rat to intraperitoneally administered nickel increased at days 12 and 19 of pregnancy with LD_{50} values ranging from 5 to 10 mg Ni/kg of body weight. When administering nickel on day 8, 12 or 16 of gestation in doses of 1.2 and 4 mg Ni/kg, malformations occurred if nickel was administered during organogenesis and at maximal severity at dose levels that were toxic to the dam. Additionally, doses resulting in a teratogenic effect during organogenesis resulted at the same time in a decreased incorporation of ^{3}Hleucine into foetal protein and an increase in maternal plasma glucose concentration. The incorporation of (^{14}C)thymidine into DNA was unchanged after administration of nickel.

5.3 Conclusions

A range of reproductive effects may be induced by nickel in experimental animal studies. However, the doses used are rather high and may not relate at all to human exposures. Further, the mechanism of the effects seen is unclear. No information on reproductive effects in humans caused by nickel has been found. Thus, at this point, reproductive effects do not seem likely to occur in humans as a result of occupational exposures if other toxic effects are prevented.

6. OTHER HEALTH EFFECTS

6.1 Biochemical effects

Nickel has a number of beneficial effects on various organisms and is, in fact, an essential nutrient, as reviewed by Anke et al. (1984). Nickel is necessary for the growth of several species of bacteria, and urease from certain plants is a nickel protein. Nickel deficiency has been demonstrated in goats, miniature pigs and rats; it results in growth retardation, skin abnormalities, anaemia, deficient carbohydrate metabolism and other changes. Although nickel deficiency has never been demonstrated in humans, minute amounts may well have some beneficial effects if nickel acts, e.g., as an essential enzyme activator.

Due to the affinity to functional groups, such as carboxyl, imidazol and amino groups, excess amounts of nickel may have adverse biochemical effects. Although studies in this area are interesting and may provide crucial information on toxicological mechanisms, the relevance to human health is limited, as similar effects have not been documented in studies in humans.

In particular, attention has focused on the nickel-induced hyperglycaemia. Thus, Horak et al. (1978) found that the hyperglycaemia induced by i.p. injection of a large dose of a soluble nickel compound was due to pancreatic release of glucagon, rather than inhibition of glycolysis.

In addition, lipid peroxidation has attracted considerable interest. Sunderman et al. (1985) found increased lipid peroxidation in several tissues (liver, kidney and lung) of rats after s.c. administration of $NiCl_2$. Increased lipid peroxidation was not observed in brain, heart, spleen or testes. A positive dose-response relationship was observed in liver and kidneys in the dose range 0.12-0.75 mmol/kg body weight (7-44 mg Ni/kg). Lipid peroxidation generates intracellular free radicals which may react with various biological targets (membranes, proteins, DNA). Increased lipid peroxidation may thus contribute both to the acute toxicity and the carcinogenicity of nickel. The molecular mechanism for nickel-induced lipid peroxidation is not known, but could conceivably involve redox processes involving the Ni(III)ion. This hypothesis would implicate both Ni(II) and Ni(III) as carcinogenic forms of nickel.

6.2 Acute manifestations

Acute nickel poisoning is rare (Raithel and Schaller, 1981). Gastroenteritis, colic, anaemia and cachexia appear to be the major signs in serious intoxication. Neurological effects, such as tremor, chorea, and convulsions have also been described. Only one case of fatal nickel intoxication has been described (Daldrup et al., 1983). A 2 1/2-year old girl ingested about 15 g of nickel sulfate crystals. On admission at the hospital, the girl was somnolent with meningeal irritation, wide and unresponsive pupils, high pulse rate, and pulmonary rhonchi on auscultation. Carciac arrest occurred after 4 h. Autopsy findings gave no clue to the rapid progression of the intoxication, but increased nickel levels were found in all tissues examined, including liver, stomach and spinal cord.

In experimental studies reviewed by Raithel and Schaller (1981) oral dosage of nickel results in gastroenteritis, salivation, respiratory disturbance, cardiac arrythmia, as well as muscular atrophy, hypoglycaemia, anaemia and oedema of the lungs, liver, kedneys, brain and meninges. Increased permeability of blood vessels, kidney tubule dysfunctions and cytotoxicity in the central nervous system were also seen in relation to increased doses of nickel. Parenteral injection of nickel may result in very similar effects.

These effects are of limited interest in occupational health, as severe intoxications are very unlikely to occur. However, the data would suggest that the lungs, the heart and the kidneys may be particularly sensitive to nickel toxicity even at lower levels.

6.3 Organ toxicity

As mentioned in section 2.7, the highest nickel concentrations after acute exposures are usually found in the kidneys. Nephrotoxicity has been induced at high acute doses in rats, resulting in proteinuria, aminoaciduria, reduction of urea clearance and histological changes (Gitlitz et al., 1975). These findings have been confirmed by Sunderman and Horak (1981) who also found a nickel-induced increase of N-acetyl-beta-D-glucosaminidase activity in the urine and of urinary valine; these parameters returned to normal levels within 9 d after nickel injection. An excess level of $beta_2$-microglobulin in urine was found in electrolytic nickel refinery workers with a urinary nickel excretion above 100 ug/l, thus indicating an effect on the proximal tubuli of the kidney (Sunderman and Horak, 1981).

Nickel has a long half-life in pulmonary tissue, and chronic effects could therefore occur. Hyperplasia of bronchiolar epithelium with peribronchial lymphocytic infiltrates and a markedly increased mucous production was induced in rats after inhalation of nickel chloride and nickel oxide at levels considered acceptable for occupational exposures (Bingham et al., 1972). More recently, Camner et al. (1984) exposed rabbits to 0.1 and 1 mg/m^3 of respirable metallic nickel dust and 0.2 mg/m^3 of nickel chloride aerosol for 1-8 months, 5 d/week, 6 h/d. Extensive abnormalities were seen, especially in macrophages and type II cells. The amount of phospholipids increased considerably and showed a change in composition, indicating a specific effect on surfactant production which may have stimulated the macrophage response. These effects were seen both with nickel metal and nickel chloride but not with iron, cobalt or chromium dust. The experimental studies were conducted with nickel exposure levels similar to those occurring in industrial settings. A similarity to pulmonary alveolar proteinosis would suggest that the pulmonary toxicity could induce increased susceptibility to infections (see section 4.3).

Sunderman (1981b) and NIOSH (1977) reviewed the literature on clinical findings of airway pathology in nickel refinery workers. Chronic rhinitis, nasal sinusitis, anosmia and, in some cases, perforations of the nasal septum have been reported. Histological changes in the nasal epithelium are reviewed in section 3.3.8. Unfortunately, the clinical relevance of pulmonary toxicity of nickel is difficult to evaluate due to the dearth of clinical information.

Nickel appears to be able to substitute for calcium and cause a competitive antagonism, especially in cardiac muscle where nickel interferes with the excitation-contraction coupling and causes reduced contractility (Rubanyi and Kovach, 1980). Nickel also causes contraction of coronary vessels in dogs (Rubanyi and Kovach, 1980; Kovach et al., 1980; Rubanyi et al., 1981b) and of other smooth muscle tissue, such as uterine muscle (Rubanyi and Balogh, 1982). In a more recent experiment (Rubanyi et al., 1981a), significant increase of coronary resistance was induced by a nickel concentration of 6 ug/l in the perfusion medium.

In this connection, it is of major interest that most patients with acute myocardial infarction develop a high serum nickel level, and that considerable hypernickelaemia in these patients may be followed by coronary vasospasm (Leach et al., 1985). The sources and mechanisms of nickel release which occurs in patients

with acute myocardial infarction or unstable angina pectoris are unknown (Leach et al., 1985), but the implications of the potential cardiotoxicity are considered so serious that Sunderman (1983) proposed that nickel levels in i.v. solutions should be kept below 5 ug/l and that the amount administered through intravenous fluids should not exceed 0.5 ug/kg/d. Although this limit in particular is meant to protect susceptible groups of hospitalized patients, possible risk groups among nickel-exposed workers may need similar protection.

6.4 Induction of erythrocytosis

Erythropoiesis is initiated by the release of an erythropoietic factor from the kidney (and perhaps other organs or tissues) acting on the differentiation process which regulates the size of the red cell pool. The resulting erythrocytosis is associated with increased haematocrit, haemoglobin and circulating erythrocyte mass values with a normal plasma volume.

Several studies have dealt with the effect on erythropoiesis of intrarenal injection of 5 mg of nickel subsulfide into each pole of the right kidney in rats. Jasmin (1973) and Jasmin and Riopelle (1976) found that erythrocytosis developed within 2 months after injection of nickel subsulfide whereas injection of nickel sulfide and metallic nickel did not induce the effect. Jasmin and Solymoss (1978) studied the dose-response relationship by injecting doses from 0.25 mg up to 5 mg Ni_3S_2 into one or both poles of a kidney. They found that 0.25 mg of Ni_3S_2 is sufficient to induce haematologic changes and that the reaction seemed unrelated to the site of injection into the kidney parenchyma or to the dose. In addition, ablation of the treated kidney reverses the erythrocytic reaction within 1 month, suggesting the presence of a humoural factor released by the nickel-injected kidney.

Oskarsson et al. (1981) studied the ability of nickel and cobalt ions as chlorides to stimulate erythropoiesis when administered by intraperitoneal infusion by osmotic minipumps. Cobalt stimulated erythropoiesis whereas nickel did not. The mechanism by which nickel causes marked erythrocytosis when administered intrarenally and not when administered intraperitoneally is unknown, and it differs from that of cobalt where i.p. administration causes erythrocytosis. Differences in the influence of hypoxia, and in the capacity to derange membrane integrity of the lysosome-rich, light mitochondrial fraction may play a role Oskarsson et al., 1981). Further, enhanced renal production of erythropoietin after i.r. injection of Ni_3S_2 may constitute an oncodevelopmental marker of neoplastic dedifferentiation (section

3.4.6).

Sunderman et al. (1982) studied the development of erythrocytosis in rats, guinea pigs, hamsters and gerbils after intrarenal injection of nickel subsulfide. They found that rats and guinea pigs developed erythrocytosis at 1-4 months after intrarenal injection of 5 mg of Ni_3S_2, whereas hamsters and gerbils did not. Implantation of Ni_3S_2 within semi-permeable cellulose tubules in equal amounts also resulted in erythrocytosis, indicating that phagocytosis of Ni_3S_2 particles is unnecessary for erythropoietic stimulation. Erythropoietin activity in rat serum increased by 6-fold at 2 weeks after intrarenal injection in contrast to the unchanged activity in pooled extracts from Ni_3S_2-treated rat kidneys.

Finally, Sunderman et al. confirmed the results of Jasmin and Solymoss (1978) that erythrocytosis in rats was completely blocked by excision of the Ni_3S_2-injected kidney and that excision of the non-treated kidney did not have any effect on the erythrocytosis. Neither treatment of the spleen of rats with Ni_3S_2 nor splenectomy had an effect on erythropoiesis. In contrast to this observation, partial inhibition of Ni_3S_2-induced erythrocytosis in rats occurred after simultaneous intrarenal injection of manganese, copper, or aluminium dusts, benzo(a)pyrene, or subcutaneous infusion of sodium diethyldithiocarbamate (DDC) which chelates the nickel ion. Erythrocytosis induced by i.r. injection of Ni_3S_2 was augmented by i.r. injection of chromium dust or intramuscular administration of iron-dextran.

Although stimulation of erythropoiesis is unlikely to occur in nickel-exposed workers, these studies are of considerable interest with regard to the toxic mechanisms of the nickel ion.

6.5 Conclusions

Nickel is an essential nutrient in several species and may, in minute amounts, have essential biochemical functions in humans. The health-related concern in regard to human nickel exposures is due to toxic effects of increased intake. Acute manifestations include symptoms and signs from the central nervous system, kidneys, heart and lungs. Only one death due to acute nickel intoxication has been recorded. Kidney toxicity mainly relates to tubular dysfunction with increased levels of small-molecular-size proteins and amino acids in the urine, as documented in experimental studies and in nickel electrolysis workers. Pulmonary effects have not been studied in detail in humans, but experimental animal data strongly indicate considerable effects of 0.1

and 0.2 mg Ni/m^3 on surfactant production, type II cells and macrophages. Nickel interferes with heart muscle and smooth muscle contraction and causes a significant increase of coronary vessel resistance even at a nickel level of 6 ug/l in the perfusion fluid.

7. PREVENTIVE STRATEGIES

7.1 Critical effects

A causal link has been established between occupational nickel exposure in primary nickel production (and perhaps elsewhere) and cancer of the nose and nasal sinuses and cancer of the lung (section 3.5.12). A causal link has also been established between cutaneous nickel exposure and a form of allergic contact dermatitis (section 4.1). In addition, nickel may cause allergic and toxic effects in the lungs (sections 4.2 and 6.3), effects on the heart due to dissolved nickel in the circulation (section 6.3), immunotoxicity (section 4.3), and additional health effects at high exposure levels.

The epidemiological evidence on carcinogenicity suffers from some important weaknesses. First of all, the airway cancers occur in only some of the workers exposed to nickel, and apparently the major risk is limited to smelter and refinery workers, especially those who have worked at the calcining and sintering operations. Sparingly soluble compounds, in particular nickel subsulfide and oxides have been implicated as possible causal agents. Excess cancer risk has also been found in other departments, but no specific nickel compound(s) has been convincingly implicated due to the problems discussed in section 3.5.1. Thus, at this point, dose-response relationships for the various forms of nickel are unavailable. Studies in experimental carcinogenesis strongly indicate that the nickel ion is the carcinogenic factor, either due to direct reaction with macromolecular or, indirectly, by induction of free radicals. No other plausible hypothesis has been convincingly supported (sections 3.3.9 and 3.4.8). Data on the uptake of nickel into the body and into cells suggest that nickel ions may not readily reach target molecules in cells (section 2.9), and different nickel compounds will have different degrees of toxicity. However, at this point, the evidence is insufficient to rate different compounds with regard to their carcinogenic potential in any accurate way.

With regard to the allergic eczema reactions caused by nickel, the situation is quite different (section 4.1). Current evidence suggests that nickel allergy usually is established during the early part of life, mostly during the teenage years and most frequently caused by dermal exposures to nickel-containing items, such as earrings. Cutaneous exposure to nickel at work may also cause development of allergy. Subsequent to the sensitization, minimal exposure to nickel may provoke the development of contact dermatitis, first at the original site of reaction, later in the

form of hand or more generalized eczema which can be incapacitating. This sequence may be seen in workers even with relatively minor dermal exposures to nickel, such as hair dressers or janitors (section 1.5). In some cases, systemic nickel exposure following absorption through the lungs or the gastrointestinal tract, may result in provocation of contact dermatitis in a nickel-allergic individual. The major objective in relation to contact dermatitis is to prevent the nickel sensitization, and the primary public health efforts are related to dermal exposures outside the occupational environment. However, limitation of skin contact with nickel and nickel compounds at work would be a prudent measure. In addition, a considerable proportion of the population is already sensitized and is likely to develop contact eczema even with minor cutaneous exposures.

In addition, soluble nickel compounds may cause systemic toxicity, in particular cardiotoxicity (section 6.3). Increased resistance of coronary vessels has been produced by nickel levels in perfusion fluid at 6 ug/l and above, levels which may be exceeded as a result of occupational exposures. Although clinical support for this experimental evidence is meagre at present, the potential health significance must be evaluated cautiously.

With regard to nickel metal and nickel-containing alloys, pulmonary deposition appears to cause a minimal, if any, carcinogenic risk or possibility of eczema provocation. However, studies on pulmonary effects of nickel (section 6.3) suggest that local toxicity occurs with possible significance for subsequent development of chronic lung diseases. Asthma and, perhaps, metal fume fever could result from freshly oxidized particles of nickel (section 4.2).

Thus, different critical effects are recognized in relation to sparingly soluble nickel compounds, easily soluble compounds and nickel metal/alloys. The significance of immunotoxic and teratogenic effects seen in experimental studies is difficult to evaluate, but these effects are not likely to occur if the above-mentioned critical effects are prevented.

Frequently, lack of convincing scientific proof for critical effects is cited as a reason not to initiate preventive action. However, in the study of causal factors in human disease, successful results of an intervention often constitute a major criterion for the proof of a causal relationship. Thus, while the intervention is likely to prevent the occurrence of a critical effect, the initiation of these efforts may be halted if the causal link has been deemed insufficient. Another paradox is that

prevention aims at reducing or removing a critical effect which is the very reminder that preventive efforts are needed. Thus, when the disease seems to be under control or only occurs rarely or after a long latent period, the need for current and improved prevention programmes may erroneously appear minimal.

The benefits of regulation are difficult to calculate: one cannot precisely identify the health benefits that will accrue in 10, 20 or 30 years from reduced exposures to toxic substances or carcinogens; the data for prediction do not exist, and causality mechanisms in occupational disease are too complex to be defined with the same certainty as the costs of a new ventilating system. The largest problem with cost-benefit analysis, however, is not lack of information - it is the impossibility of weighing lives spared against the dollar costs for prevention (Bingham, 1985).

7.2 Exposure monitoring and control

The most efficient preventive strategy is to regulate the hazard at the source. If the exposure cannot be abated, the emissions must be kept at or below a level recognized as being without any risk to health. Exposure monitoring and engineering control should therefore be the mainstay of the prevention.

Exposure limits are generally used in this connection, but no agreement on the level of these limits has been reached on an international scale (Table 20).

Unfortunately, the criteria or basis used for the standard-setting in different countries are only available to a limited extent. Thus, in the Federal Republic of Germany, a summary is available (MAK-Werten. Nickel und Nickelverbindungen, 1971) According to this document, nickel metal, nickel sulfide or sulfide ores, nickel oxide and nickel carbonate, as they occur during production and use, are considered carcinogenic. Thus, no exposure limit (MAK) has been determined, only a technical guideline. Due to the risk of sensibilization caused by nickel metal and soluble compounds, nickel has received a "skin" denotation.

In the USA, ACGIH (1984) has published the background material for the Threshold Limit Values. Following a brief review of major studies considered, ACGIH concludes: "With the available knowledge, it is not felt that all forms of nickel are carcinogenic. Therefore, a TLV of 1.0 mg/m^3 is recommended for nickel metal and insoluble inorganic nickel compounds. A TLV of 0.1 mg/m^3 and a STEL of 0.3 mg/m^3 are recommended for soluble nickel compounds." Unfortunately, the basic criteria used when reaching this con-

clusion are not stated although the limit for sparingly soluble nickel compounds is intended to protect against carcinogenic effects and the limit for soluble compounds against sensitization. In addition, nickel sulfide roasting, dust and fume were considered separately, and it is stated: "In 1960, fluid-bed roasting was introduced at Sudbury. This led to control of atmospheric levels to around 1 mg/m^3 as nickel fume and dust. In the 15 years (1960-1975) that have since elapsed, no cancers attributed to nickel have appeared among employees in this operation. As 15 years is insufficient time to determine the appropriateness of the 1.0 mg/m^3 limit for the prevention of nickel cancers, this TLV should be used with caution." In this case, a limit has been set at a level which may not offer full protection against carcinogenic effects.

NIOSH (1977) concluded: "In the absence of adequate information on the amount of inorganic nickel that can be inhaled over a working lifetime without an excess risk of cancer, it is proposed to recommend a permissible limit based on the lowest TWA concentration of nickel reliably detectable over a single work shift." A limit of 15 ug/m^3 was then proposed.

A Dutch Working Group of Experts concluded in a draft document that experimental evidence suggested a threshold for non-harmful effects below 0.2-0.3 mg/m^3 (6 h/d, 6 weeks) for soluble nickel compounds and below 0.1 mg/m^3 for nickel metal dust. They therefore recommended an exposure limit for nickel metal, inorganic compounds and industrial nickel oxide (except primary nickel production) of 50 ug/m^3 as an 8-h limit and 100 ug/m^3 as a ceiling value for 15-min exposures. On the basis of carcinogenic effects, the experts followed the NIOSH recommendation and suggested limits of 10 ug/m^3 (8 h) and 20 ug/m^3 (15 min) for primary nickel production (Working Group of Experts of the National Maximum Workplace Concentration Committee, 1985).

The available evidence strongly indicates that nickel oxide and crystalline compounds, such as nickel subsulfide, as they occur in primary nickel smelters and refineries, are more potent carcinogens than other nickel compounds. A prudent effort would therefore be to keep exposures to these compounds at the lowest level reasonably achievable. On the other hand, exposures to amorphous nickel compounds, nickel ore, ore concentrate, nickel metal and alloys are not considered as hazardous, and a less strict exposure limit could be accepted. Soluble compounds may result in acute airway symptoms and, in particular, very high nickel levels in serum and urine, which could in some cases elicit an eczema outbreak in a sensitized individual, although

such cases appear to be rare. The relation of high serum nickel levels to cardiotoxicity, immunotoxicity and other adverse effects is far from clear. However, maintaining a low serum nickel as a result of exposures to soluble compounds would be a prudent measure.

When examining the exposure limits in various countries, the Norwegian limits are of particular interest. These limits apply to a large refinery, mines (at least in principle) and a range of nickel-using industries. The same exposure limit at (0.1 mg/m^3) has been set for both soluble and insoluble nickel compounds, a decision which is less difficult to implement than several sets of standards. However, the feasability of a lower limit for primary nickel production should be evaluated. In addition, the need for prevention of cutaneous exposures, especially to soluble nickel compounds, must be emphasized.

7.3 Biological monitoring

Biological monitoring is a useful part of biomedical surveillance as a supplement to other preventive efforts. The Advisory Council (ACOHOS, 1985) has defined the use and discussed the advantages and limitations in a broader sense.

By measuring the nickel levels in urine and/or serum, the absorbed nickel dose rather than the exposure is estimated. Thus, biological monitoring should ideally contribute: 1) early warning signals allowing reduction or elimination of excess exposures before irreversible adverse effect have been induced; 2) overall exposure indices in various exposure groups and industrial settings, allowing quantitative risk estimation for adverse health effects, if present; and 3) an efficient routine control system assuring that implemented exposure limits are effective.

However, the use of biological monitoring is only meaningful when the following requirements have been fulfilled: 1) a relevant sample can be obtained and related to the kinetic behaviour of nickel in the body; 2) the sampling and analytical procedures are valid and result in valid determinations of the nickel concentrations; 3) the "normal" range of nickel concentrations is known from individuals without occupational exposures; and 4) the results obtained must be evaluated by comparison to relevant dose-effect and dose-response relationships, so that an appropriate risk assessment will be possible. These requirements are only partially fulfilled with regard to various forms of nickel (section 2).

Biological monitoring for nickel exposure may employ the following samples: whole blood, plasma/serum, urine, faeces, hair, nasal sinus biopsies, and various autopsy materials. In occupational health, plasma/serum and urine samples are most useful.

Due to improved sampling, reduced contamination and improved analytical technology, reference values for nickel in biological fluids of healthy non-exposed individuals have decreased steadily during recent years. Representative values are 0.34 $\pm$ 0.28 ug/l blood, 0.28 $\pm$ 0.24 ug/l serum (Linden et al., 1985), and 2.0 $\pm$ 1.5 ug/g creatinine in urine (spot collection) (Sunderman et al., 1986).

Body fluid levels generally reflect recent exposures (the past few days) to soluble or relatively soluble nickel compounds; half-times of plasma nickel in a group of nickel platers after exposure to soluble nickel were found to be between 20 and 34 hours, and the half-times for urinary nickel were between 17 and 39 hours in the same individuals (Tossavainen et al., 1980). Comparable urinary half-times were observed after exposure to less soluble forms of nickel in the glass industry (Raithel et al., 1982) and during welding (Zober et al., 1984). However, after (pulmonary) exposure to sparingly soluble compounds, nickel will only be slowly released from the lungs, and the serum or urine levels will then rather reflect the accumulated lung burden rather than recent exposure. Thus, even 3-4 years after cessation of exposure, nickel levels in plasma and urine were elevated in retired nickel workers exposed to sparingly soluble compounds in the roasting/smelting department (Boysen et al., 1984).

A number of studies (Table 21, Fig. 2) demonstrate a positive relation between air levels of nickel and serum/plasma levels of nickel after occupational exposure to various (insoluble, mixed or soluble) forms of nickel. The air levels of nickel varied by three orders of magnitude, and serum/plasma nickel levels varied by about 30-fold within and between these studies. However, the somewhat scattered observations cannot be used for any accurate predictions of air levels from serum/plasma concentrations or vice versa.

When occupational nickel exposure includes both easily and sparingly soluble compounds, urinary nickel levels will mainly reflect the exposure to the soluble compounds, since exposure to less soluble forms of nickel result in much smaller elevations at the same air levels of nickel (Table 21, Fig. 3). Again, the total data base demonstrates a positive, though scattered relation between air and urinary levels of nickel. For example, the

same air level may result in urinary levels varying up to 2 orders of magnitude.

Even when looking solely at "pure" exposures to soluble nickel compounds, one does not find a strong correlation between air levels and urinary levels of nickel (Fig. 3). Figs 4 and 5 demonstrate a positive relation between serum/plasma and urinary nickel levels.

The use of urine samples for monitoring the exposure to (mainly soluble) nickel compounds offers certain advantages compared to serum or plasma, as the concentrations are usually much higher, most frequently 2-15 times higher (Figs 4 and 5) (Morgan and Rouge, 1984; Hogetveit et al., 1978; Torjussen and Andersen, 1979; Zwennis and Franssen, 1983; Zober et al., 1984b; Raithel et al., 1985). In these studies, average serum or plasma nickel concentrations were given in ug/l, while average urine concentrations were given either in ug/l or ug/g creatinin (the average normal urinary creatinin concentration is about 1.3 g/l).

Normalization to adjust for variable urine dilution can be performed by expressing the results as ug nickel per g of creatinin or by adjustment to a normal specific gravity (Morgan and Rouge, 1984; Adams, 1980; Sunderman et al., 1986). However, these parameters may not necessarily reflect the changes in nickel levels with variations in urinary flow rates, and very dilute urine samples are particularly likely to cause erroneous results. Such samples should be discarded.

The best indicator of current exposure to soluble nickel compounds is a 24 h urine sample. Such sampling is, however, seldom applicable in routine biological monitoring of occupational exposure. The alternatives are venipuncture or sampling of spot urines in a uniform way (e.g. post-shift). Due to the rapid clearance of the soluble part of inhaled nickel, sampling should preferably be performed on one of the last work-days of the week.

Thus, evaluation of carcinogenic risks associated with nickel levels in body fluids is difficult, if not impossible, because pulmonary exposure to sparingly soluble nickel is of prime interest in relation to lung cancer risk. Measurement of total airborne nickel in combination with detailed information about the industrial process and the nickel compounds generated may contribute data more relevant for risk evaluation in this regard.

Even though the procedures used for biological monitoring may not reflect the exact respiratory exposure levels, the monitoring of

nickel concentrations in body fluids may be warranted to ensure that individual doses absorbed are at an acceptable level. Thus, as discussed in section 6.3, nickel may cause systemic effects, in particular on the heart: in experimental studies, coronary vessel contraction has been shown at nickel levels of 6 ug/l and above. Thus, a limit for plasma/serum nickel of 5 ug/l, as proposed (on the basis of other considerations) by Barton and Hogetveit (1980) would seem reasonable.

The results of biological monitoring must be evaluated in relation to other medical information. Thus, patients with prior heart disease or kidney disease may be more susceptible to increased circulating levels of nickel. On the other hand, haemodialysis as such may cause increased serum nickel values (Hopfer et al., 1985), and some drugs, such as disulfiram which is metabolized to diethyldithiocarbamate (see section 2.3), may result in high nickel concentrations in serum. The relevance of environmental exposures to nickel (section 1.5) and possible release from, e.g., orthopaedic implants must also be evaluated.

Therefore, when the nickel species in the exposure are known and sampling follows meaningful principles, analysis of nickel in urine or serum/plasma may be a useful supporting parameter, provided that the above caveats are respected. Thus, biological monitoring should be made available as a voluntary test at intervals which depend on the exposure level and the nickel compounds in question.

7.4 Health surveillance

The Advisory Council (ACOHOS, 1985) defined health surveillance as "the continuing scrutiny of specific worker sub-groups for the purpose of identifying disorders or health states. Health surveillance involves procedures such as laboratory testing and detailed clinical examinations which evaluate physiological changes and/or evidence of pathology, allowing for a more detailed diagnosis of health conditions."

In agreement with this definition, three components may be identified: 1) the detection of adverse effects of workplace exposures, including both recognized and as yet unanticipated effects; 2) the detection of evidence of internal human exposure to a toxic agent, 3) the detection of host-related factors in exposed persons that might place them at increased risk of suffering adverse effects from workplace exposures (Ordin and Levin, 1985). However, some overlapping with health screening and biological monitoring, as outlined by the Advisory Council (ACOHOS,

1985) may occur. Criteria for selection of such screening procedures (Wilson and Jungner, 1968) and early detection of disease (WHO, 1975) have been widely accepted.

Evidence of carcinogenic risk may be obtained by examination of cultured human cells, e.g., peripheral lymphocytes. Breaks, gaps and sister chromatid exchange are relevant parameters which may be assessed by routine procedures (Waksvik et al., 1984). However, as discussed in sections 3.3.5 and 3.3.6, the results obtained do not entirely elucidate the relation to exposure to various nickel species, and dose-response relationships are inaccurate, at best. Also, as discussed in section 2.9, the cellular uptake mechanisms may vary, and a genotoxic effect in peripheral lymphocytes may not necessarily reflect a carcinogenic effect elsewhere in the body.

Extensive studies at a Norwegian nickel refinery have contributed significantly to the evaluation of nasal biopsies for early detection of sinonasal cancer, as discussed in section 3.3.8. The biopsy is taken from the middle turbinate (Torjussen, 1979), but the possible occurrence of epithelial changes elsewhere in the nasal mucosa would probably require that several biopsies are obtained in order to avoid false negative results. Loss of respiratory epithelium and development of squamous metaplasia is regarded as an early, nonspecific change (Torjussen et al., 1979a,b). Dysplasia, carcinoma in situ and frank carcinoma should lead to subsequent diagnostic procedures and surgical removal (Barton and Hogetveit, 1980). Although the mechanism and pathogenesis are incompletely understood, the use of nasal biopsies has proven useful in the prevention of more serious disease and death due to this cancer type. However, the studies published only deal with subjects with heavy exposures to nickel at a refinery and a recognized high risk of developing nasal cancer. The diagnostic validity of the test is unknown. Nasal biopsy is unpleasant to the patient, requires special skills and has only proven useful in patients at high risk. Thus, nasal biopsy should only be offered as a voluntary test for workers with past heavy exposures associated with an increased risk of nasal cancer.

Exfoliative cytology of nasal mucosa may be used for early diagnosis and for screening (Voss et al., 1985), but more extensive experience is necessary before the usefulness and validity of this test can be determined.

With regard to lung cancer, two procedures may be considered: sputum cytology and chest X-ray. These tests may detect early, non-symptomatic lung cancer, and their validity and benefits with

regard to long-term survival of the patient are currently being evaluated (WHO, 1982). A pilot programme using sputum cytology has been implemented at a nickel-producing plant in Sudbury, Ontario (see section 3.3.8). Although the preliminary findings are optimistic, the long-term significance remains to be determined. Sputum cytology and chest X-ray examination may only identify lung cancers at a stage when treatment will only affect long-term survival to a minimal extent, if at all. Also, such tests may distract from such major preventive efforts as smoking cessation and abatement of respiratory nickel exposure. In agreement with the World Health Organization (WHO, 1982) and American Cancer Society (1980), these procedures cannot be recommended as mandatory health surveillance tests. However, research in this area is important, and a continuation of, e.g., sputum cytology as a prospective epidemiological study would be of considerable scientific interest and potential health benefit.

On the basis of such considerations and the general requirements for health surveillance of workers exposed to occupational hazards, Bishop (1985) suggested the following items for the initial assessment of new employees in the nickel industry:

- a detailed occupational history and a full clinical history with specific reference to atopy, skin conditions e.g. dermatitis and eczema, and any upper and lower respiratory tract complaints.

- a smoking and family history should be noted.

- an assessment of the individual's ability to wear respiratory protection where this is necessary should be carried out.

- consideration should be given as to whether a base-line chest X-ray is of any use.

- skin testing is not advisable for initial assessment and detailed questioning is preferable.

- where it is considered that there is an increased risk of allergic asthma a validated respiratory questionnaire and base-line spirometry may be of use.

- the value of biological monitoring should be given very careful consideration by the medical officer prior to its institution, and baseline levels may be obtained.

Subsequent, periodic assessments should include:

- the reporting of skin and respiratory symptoms and any other complaints which the worker considers attributable to nickel compounds to the medical department should be encouraged.

- a periodic assessment of sickness absence records with special note of respiratory and skin conditions could be undertaken and any trends or patterns in sickness absence noted and investigated

- an individual worker should be reviewed on return to work after prolonged sickness absence (i.e., 1 month) and an assessment made of his fitness to continue work with nickel compounds

- individuals who develop contact dermatitis should be skin tested and if positive for nickel, concideration should be given to removal from exposure and to alternative employment where this is available

- where it is considered that an increased risk of allergic asthma exists, a validated respiratory questionnaire may be applied annually and periodic spirometry where indicated

- individuals who require further investigation should be referred to their family practitioner with their consent.

These suggestions are quite similar to those recommended by NIOSH (1977). In addition to the items mentioned, examination of the cardiovascular system would seem indicated and should include blood pressure, auscultation, pulse and relevant data on family history and symptoms. If increased exposures occur or are suspected, the kidney function should be assessed, e.g., by including an analysis of beta$_2$-microglobulin in urine. Further, requirements for the maintainance and storage of records, confidentiality issues, worker information and education are necessary.

7.5 Conclusions

In the absence of detailed dose-response relationships and definite thresholds, exposure levels for nickel and inorganic nickel compounds should be kept as low as reasonably achievable. An exposure level no higher than 0.1 mg/m^3 (as nickel) is likely to protect against most adverse effects, although a lower level would be indicated for the nickel-producing industry. Skin con-

tact should be limited, and dermal exposure to soluble nickel compounds should be prevented. As some effects are related to circulating, dissolved nickel in the body, biological monitoring of serum/plasma nickel levels should be offered as part of a health surveillance programme, and the nickel levels should be kept below 5 ug/l serum or plasma. Neither chest X-ray nor sputum cytology can be considered obligatory items, but nasal biopsy or exfoliative cytology should be offered to employees with high exposures in the past. The health surveillance should emphasize early detection of possible effects on lungs, heart, kidneys and skin.

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Table 1: Physical constants of the element nickel.

Atomic number	28
Atomic weight	58.71
Natural isotopes	58, 60, 61, 62, 64
CAS number	7440-02-0
Melting point (^{o}C)	1453
Boiling point (^{o}C)	2732
Density at 20^{o}C (g/cm^3)	8.908

Table 2: Nickel alloys.

Name/trade name	CAS no.	Ni content (wt.%)	Other metals	Melting range °C
B-1900	12773-54-5	64.0	Co,Cr,Mo, Al,Ta,Ti,Zr	1275-1300
Hastelloy Alloy B-2	61608-60-4	65.4	Mo,Fe,Co, Cr,Mn	1320-1350
Hastelloy Alloy G	39367-32-3	42.0	Cr,Fe,Mo, Co,Cu,Nb, Ta,Mn,W	1260-1343
Haselloy Alloy C-276	12604-59-0	55.4	Mo,Cr,Fe, W,Co,Mn	1323-1371
Incoloy Alloy 800	11121-96-3	32.5	Fe,Cr,Mn, Al,Ti	1355-1385
Inconel Alloy 600	12606-02-9	76.0	Cr,Fe,Mn	1355-1415
Inconel Alloy 718	12606-10-9	52.5	Cr,Fe,Nb, Mo,Ti,Al,Mn	1260-1335
Inconel Alloy 754	62112-97-4	78.0	Cr,Ti,Y, Al	1320-1390
Mar-M200	12604-85-2	60.0	W,Co,Cr, Al,Ti,Nb,Zr	1315-1370
Monel Alloy 400	11105-19-4	66.5	Cu,Fe,Mn	1299-1349
Monel Alloy K-500	11105-28-5	65.0	Cu,Al,Fe, Mn,Ti	1316-1349
Nichrome	12605-70-8	77.0	Cr,Mn,Fe	1399
Nickel 200	12671-92-0	99.5	Mn,Fe,Cu	1435-1446
Nickel-gallium alloy	-	60.0	Ga	-
Nimonic Alloy 80A	11068-71-6	76.0	Cr,Ti,Al, Mn,Zr	1360-1390
Nimonic Alloy 115	51204-21-8	60.0	Cr,Co,Al, Ti,Zr,B	-
Rene 41	11068-84-1	55.0	Cr,Co,Mo, Ti,Al,B	1315-1370
Udimet 200	12616-78-3	42.7	Fe,Cr,Mo, Ti,Mn,Al	1229-1416
Udimet 500	11068-87-4	54.0	Co,Cr,Mo, Al,Ti,Zr	1300-1395
Udimet 700	11068-91-0	53.0	Co,Cr,Mo, Al,Ti,B	1205-1400
Waspaloy	11068-93-2	58.0	Cr,Co,Mo, Ti,Al,Zr	1330-1355

Table 3: Chemical identity, physical properties, solubilities and uses of inorganic nickel compounds.

CAS no.	Chemical name	Chemical formula	Molecular weight	Density	Melting point (°C)	Solubility in water g/100 ml[x]	Solubility in other solvents	Uses
373-02-4	Nickel acetate	$Ni(CH_3COO)_2$	176.80	1.798	d	16.6	acetic acid	catalyst, pigment
6018-89-9	Nickel acetate, tetrahydrate	$Ni(CH_3COO)_2 \cdot 4H_2O$	248.86	1.744	d	16	alcohol	plating, pigment
16122-03-5	Ammonium nickel chloride, hexahydrate	$NH_4NiCl_3 \cdot 6H_2O$	291.20	1.645	-	vs	-	plating, pigment
15699-18-0	Ammonium nickel sulfate, hexahydrate	$(NH_4)_2Ni(SO_4)_2 \cdot 6H_2O$	395.00	1.923	-	10.4 30 (80°C)	ammonium sulfate	plating
12035-52-8	Nickel antimonide	NiSb	180.45	7.54	1158	i	-	-
27016-75-7	Nickel arsenide	NiAs	133.62	7.57	968	i	nitric acid Aqua Regia	-
12255-80-0	Pentanickel diarsenide	Ni_5As_2	433.39	8.61	993	i	nitric acid Aqua Regia	-
12044-65-4	Undecanickel octaarsenide	$Ni_{11}As_8$	1245.19	7.95	1000	i	nitric acid Aqua Regia	-
12255-10-6 12255-11-7	Nickel arsenide sulfide	NiAsS	165.7	5.966	-	i	nitric acid Aqua Regia	-
13477-70-8	Nickel arsenate	$Ni_3(AsO_4)_2$	453.89	4.98	-	i	acid	catalyst
7784-48-7	Nickel arsenate, octahydrate	$Ni_3(AsO_4)_2 \cdot 8H_2O$	598.01	4.982	d	i	acid	catalyst

Table 3 continued.

CAS no.	Chemical name	Chemical formula	Molecular weight	Density	Melting point (°C)	Solubility in water g/100 ml[x]	Solubility in other solvents	Uses
12007-00-1	Nickel boride	NiB	69.52	7.39	d	d	nitric acid, Aqua regia	prisms
13477-93-5	Nickel bromate, hexahydrate	$Ni(BrO_3)_2 \cdot 6H_2O$	422.62	2.575	d	28	-	-
13462-88-9	Nickel bromide	$NiBr_2$	218.53	5.098	963	112.8 (0°C) 155.1 (100°C)	alcohols, ether, ammonia/ water	
7789-49-3	Nickel bromide, trihydrate	$NiBr_2 \cdot 3H_2O$	272.57	-	300 d	199 (0°C) 315.7 (100°C)	alcohol, ether, ammonia/ water	sedative
18721-96-5	Nickel bromide, hexahydrate	$NiBr_2 \cdot 6H_2O$	326.63	-	-	85	-	plating, catalyst
3333-67-3	Nickel carbonate	$NiCO_3$	118.72	2.6	d	0.009 (25°C)	acid	catalyst, plating, pigment
12607-70-4	Dinickel carbonate dihydroxide	$Ni_2CO_3(OH)_2$	210.42	-	-	i	-	-
39430-27-8	Trinickel carbonate tetrahydroxide, tetrahydrate	$Ni_3CO_3(OH)_4 \cdot 4H_2O$	304.17	2.6	-	i	hydrochloric acid, ammonia/water	pigment, plating, catalyst

Table 3 continued

CAS no.	Chemical name	Chemical formula	Molecular weight	Density	Melting point (°C)	Solubility in water g/100 ml[x]	Solubility in other solvents	Uses
12122-15-5	Pentanickel dicarbonate hexahydroxide, tetrahydrate	$Ni_5(CO_3)_2(OH)_6 \cdot 4H_2O$	587.67	-	-	i	-	catalyst, plating
39380-74-0	Pentanickel tricarbonate tetrahydroxide, tetrahydrate	$Ni_5(CO_3)_3(OH)_4 \cdot 4H_2O$	613.65	-	d	i	ammonium salts acid	-
67952-43-6	Nickel chlorate, hexahydrate	$Ni(ClO_3)_2 \cdot 6H_2O$	333.70	2.07	80 d	131 (18°C)	-	-
13520-61-1	Nickel perchlorate, hexahydrate	$Ni(ClO_4)_2 \cdot 6H_2O$	365.70	2.25	140	110.1	alcohols, acetone, chloroform	-
7718-54-9	Nickel chloride	$NiCl_2$	129.62	3.55	993 subl. 1001 (sealed)	84.2 87.6 (100°C)	alcohols, ammonia/ water, hydrazine	catalyst, pigment, gas adsorbant
7791-20-0	Nickel chloride, hexahydrate	$NiCl_2 \cdot 6H_2O$	237.70	-	-	254 599 (100°C)	alcohol	plating
12018-18-7	Nickel chromate	$NiCrO_4$	174.71	-	-	i	nitric acid, Aqua Regia, H_2O_2	plating
557-19-7	Nickel cyanide	$Ni(CN)_2$	110.75	2.39	-	0.06 (18°C)	KCN	catalyst, plating

Table 3 continued

CAS no.	Chemical name	Chemical formula	Molecular weight	Density	Melting point (°C)	Solubility in water g/100 ml[x]	Solubility in other solvents	Uses
20427-77-4	Nickel cyanide, tetrahydrate	$Ni(CN)_2 \cdot 4H_2O$	182.77	-	200 d	i	KCN, ammonia/water	metallurgy
14376-10-4	Nickel(II) hexacyanoferrat(II), undecahydrate	$Ni_2Fe(CN)_6 \cdot 11H_2O$	527.44	1.892	-	s	-	-
14220-17-8	Potassium tetracyanoniccolate, hydrate	$K_2(Ni(CN)_4) \cdot H_2O$	258.97	1.875	100 d	s	-	-
10028-18-9	Nickel fluoride	NiF_2	96.71	4.63	1000 d	4 (25°C)	HF, KF	batteries
13940-83-5	Nickel fluoride, tetrahydrate	$NiF_2 \cdot 4H_2O$	168.79	-	-	2.5	HF, KF	batteries
15684-36-3	Nickel tetrafluoroborate	$Ni(BF_4)_2$	232.25	-	d	vs	-	-
14708-14-6	Nickel tetrafluoroborate, hexahydrate	$Ni(BF_4)_2 \cdot 6H_2O$	340.37	-	-	vs	-	plating
26043-11-8	Nickel hexafluorosilicate	$NiSiF_6$	200.80	-	-	vs	-	-
26045-73-8	Nickel hexafluorosilicate, hexahydrate	$NiSiF_6 \cdot 6H_2O$	308.88	2.134	d	vs	-	-

Table 3 continued.

CAS no.	Chemical name	Chemical formula	Molecular weight	Density	Melting point (°C)	Solubility in water g/100 ml[x]	Solubility in other solvents	Uses
3349-06-2	Nickel formate, dihydrate	$Ni(HCOO)_2 \cdot 2H_2O$	184.78	2.154	200 d	s	-	catalyst
12054-48-7	Nickel(II) hydroxide	$Ni(OH)_2$	92.72	4.15	230 d	0.013	ammonia/ water acid	batteries, synthesis of Ni salts/ catalysts
12125-56-3	Nickel(III) hydroxide	$Ni(OH)_3$	109.74	-	-	i	-	-
13477-98-0	Nickel iodate	$Ni(IO_3)_2$	408.52	5.07	-	1.1 (30°C)	-	-
13462-90-3	Nickel iodide	NiI_2	312.52	5.834	797	124.2 (0°C) 188.2 (100°C)	alcohol	catalyst
7790-34-3	Nickel iodide, hexahydrate	$NiI_2 \cdot 6H_2O$	420.64	-	-	144 (25°C)	-	-
13138-45-9	Nickel nitrate	$Ni(NO_3)_2$	182.73	-	-	48.5	glycol hydrazine	-
13478-00-7	Nickel nitrate, hexahydrate	$Ni(NO_3)_2 \cdot 6H_2O$	290.81	2.05	56.7	238.5 (0°C) 150	alcohol ammonia/ water	plating, pigment, catalyst, batteries
547-67-1	Nickel oxalate, dihydrate	$Ni(COO)_2 \cdot 2H_2O$	182.76	-	-	0.004	-	Ni salts, catalyst

Table 3 continued

CAS no.	Chemical name	Chemical formula	Molecular weight	Density	Melting point (°C)	Solubility in water g/100 ml[x]	Solubility in other solvents	Uses
1313-99-1	Nickel(II) oxide	NiO	74.71	6.67 7.45	1984 2090	0.00011	ammonia/ water acid	electrodes, Ni salts, alloy, pigment
12035-36-8	Nickel(IV) oxide	NiO_2	90.71	-	-	i	acid	oxidations
1314-06-3	Nickel(III) oxide (dihydrate?)	$Ni_2O_3(\cdot 2H_2O?)$	165.42	4.83	600 d	i	ammonia/ water acid, KCN	batteries
10381-36-9	Nickel phosphate	$Ni_3(PO_4)_2$	366.04	-	-	i	-	-
14396-43-1	Nickel phosphate, octahydrate	$Ni_3(PO_4)_2 \cdot 8H_2O$	510.20	-	d	i	alcohol, acid ammonium salts	plating pigment
12035-64-2	Dinickel phosphide	Ni_2P	148.36	6.31	1112	i	nitric acid HF	-
12137-11-0	Trinickel diphosphide	Ni_3P_2	238.08	5.99	-	i	nitric acid	-
10294-65-2	Nickel potassium sulfate, hexahydrate	$NiK(SO_4)_3$	437.11	2.124	<100 d	7 (0°C) 12.3 60.8 (75°C)	-	-
1314-05-2	Nickel selenide	NiSe	137.67	8.46	-	i	nitric acid, Aqua Regia, bromine/ water	-

Table 3 continued.

CAS no.	Chemical name	Chemical formula	Molecular weight	Density	Melting point (°C)	Solubility in water g/100 ml[x]	Solubility in other solvents	Uses
12137-13-2	Trinickel diselenide	Ni_3Se_2	334.05	7.2	-	i	nitric acid, Aqua Regia	-
15060-62-5	Nickel selenate, hexahydrate	$NiSeO_4 \cdot 6H_2O$	309.76	2.314	-	40	-	-
12059-14-2	Nickel silicide	Ni_2Si	145.51	7.2	1309	i	-	-
12035-38-0	Nickel stannate	$NiSnO_3$	225.40	-	-	-	-	pigment
13770-89-3	Nickel sulfamate	$Ni(SO_3NH_2)_2$	250.90	-	500 d	s	-	plating
83458-16-6	Nickel sulfamate, dihydrate	$Ni(SO_3NH_2)_2 \cdot 2H_2O$	286.94	-	-	60	-	plating
57306-34-0	Nickel sulfamate, tetrahydrate	$Ni(SO_3NH_2)_2 \cdot 4H_2O$	322.74	-	-	s	-	plating
7786-81-4	Nickel sulfate	$NiSO_4$	154.78	3.68	848 d	30 83.7 (100°C)	alcohols	plating, pigment, catalyst, food additive, metal blackener
10101-97-0	Nickel sulfate, hexahydrate	$NiSO_4 \cdot 6H_2O$	262.86[xx]	2.07 2.03	53.3 (alpha) 103 d 280 d 800 d	40.1 340.7 (100°C)	alcohol, ammonia/ water	plating, pigment, catalyst, chemical analysis

Table 3 continued.

CAS no.	Chemical name	Chemical formula	Molecular weight	Density	Melting point (°C)	Solubility in water g/100 ml[x]	Solubility in other solvents	Uses
10101-98-1	Nickel sulfate, heptahydrate	$NiSO_4 \cdot 7H_2O$	280.88	1.948	31.5 d 99	75.6 (16°C) 475.8 (100°C)	alcohol	pigment, food additive, catalyst
16812-54-7	Nickel sulfide	NiS	90.77	5.3 5.65	797	0.00036 (beta)	nitric acid, Aqua Regia, KHS	-
12035-72-2	Nickel subsulfide	Ni_3S_2	240.26	5.82	790	i	nitric acid, Aqua Regia	-
12137-12-1	Trinickel tetrasulfide	Ni_3S_4	304.31	4.7	-	i	nitric acid, Aqua Regia	-
12035-50-6 12035-51-7	Nickel disulfide	NiS_2	-	-	400 d	i	nitric acid, Aqua Regia	-
24508-63-2	Nickel sulfite, hexahydrate	$NiSO_3 \cdot 6H_2O$	246.86	-	-	i	sulfuric acid, hydrochloric acid	-
12142-88-0	Nickel telluride	NiTe	186.31	8.50	600-900 d	i	nitric acid, Aqua Regia bromine/ water	-
12035-39-1	Nickel titanate	$NiTiO_3$	144.61	-	1000 d	i	-	pigment
706-92-93-2	Nickel zirconate	$NiZrO_3$	197.93	-	-	i	-	batteries

Table 3 continued

xx = By error Sax give Mw 449.33 and bruttoformula O_4SHNi_6
d = decomposing
i = insoluble
s = soluble
vs = very soluble
x at 20°C

Sources to table 3:

Chemical Abstracts on line search; Gmelin, 1966-67; IARC, 1976; Kirk Othmer, 1981; Linke, 1965; NIOSH, 1977; Neumuller, 1985; Sax, 1984; Sidgwick, 1950; Stephen and Stephen, 1963; Ullman, 1979; Weast, 1980-81; Windholz, 1976.

Table 4: Nickel-containing minerals.

Name	Chemical composition
Breithauptite	NiSb
Niccolite	NiAs
Zaratite	$NiCO_3$ $2Ni(OH)_2$ x $4H_2O$
Bunsenite	NiO
Morenosite	$NiSO_4$ x $7H_2O$
Millerite	NiS
Polydomite	Ni_3S_4
Heazlewoodite	Ni_3S_2
Pentlandite	$(Ni, Fe)_9S_8$
Pyrrhotite	Fe_nS_{n+1} (3-5% Ni)
Garnierite	(Ni, Mg) SiO_3 x nH_2O

Table 5: Occupations with potential exposure to nickel (revised from NIOSH, 1977).

Battery makers, storage	Nickel miners
Catalyst workers	Nickel refiners
Cemented-carbide makers	Nickel smelters
Ceramic makers	Nickel workers
Chemists	
Disinfectant makers	Oil hydrogenators
Dyers	Organic chemical synthesizers
Electroplaters	Paint makers
Enamelers	Penpoint makers
Gas-mask makers	Petroleum-refinery workers
Ink makers	Spark-plug makers
Jewelers	Stainless-steel makers
Magnet makers	Textile dyers
Metallizers	Vacuum-tube makers
Mond-process workers	Varnish makers
Nickel-alloy makers	Welders

Table 6: Workers potentially exposed to nickel in Ontario industries (data from Acres, 1982).

Occupational groups	Approximate number
Nickel production:	
Mines	8,600
Mills	1,000
Smelters	2,500
Refineries	1,300
Research laboratories	200
Other	2,600
Subtotal	16,200
Nickel-consuming industries:	
Alloy steel production	3,300
Foundries	2,100
Electroplating	2,700
Welding	500
Other	300
Subtotal	8,900
Total number exposed	25,100

Table 7: Distribution of ^{63}Ni in Tissues of Rodents.

Authors	Animal group size	Dose[a]	Relative Distribution of ^{63}Ni
Wase et al., 1954	Mouse, 8	6.2 mg/kg One ip dose	Kidney > lung > plasma > liver > erythrocyte > spleen > bladder > heart > brain > carcass (muscle, bone, and fat)
Smith and Hackley, 1968	Rat, 4	6/7 ug/kg One iv dose	Kidney > lung > adrenal > ovary > heart = gastrointestinal tract > skin > eye > pancreas > spleen = liver > muscle > teeth > bone > brain = fat
Clary, 1975	Guinea Pig, 6	1 mg/kg Sc for 5 days	Kidney > pituitary > lung > liver > spleen > heart > adrenal > testis > pancreas > medulla > oblongata = cerebrum = cerebellum
Parker and Sunderman, 1974	Rabbit, 3	240 ug/kg One iv injection	Kidney > pituitary > serum > whole blood > skin > lung > heart > testis > pancreas > adrenal > duodenum > bone > spleen > liver > muscle > spinal cord > cerebellum > medulla oblongata = hypothalamus
Herlant-Peers et al., 1982	Mouse, 4	1 ug (50 uCi ^{63}Ni/animal one ip dose[f]	Kidney > lung > uterus > skin > stomach > liver > muscle

Table 7 continued.

Authors	Animal, group size	Dose[a]	Relative Distribution of ^{63}Ni
Parker and Sunderman, 1974	Rabbit, 4	4.5 ug/kg Iv for 34-38 days[b]	Kidney > pituitary > spleen > lung > skin > testis > serum = pancreas = adrenal > sclerae > duodenum = liver > whole blood > heart > bone > iris > muscle > cornea = cerebellum = hypothalamus > medulla oblongata > spinal cord > retina > lens > vitreous humor
Oskarsson and Tjalve, 1979a	Mouse, 3	4.6 ug Ni/kg (1.2 uCi ^{63}Ni/ animal). One iv dose[c]	Kidney > lung > sternal > cartilage > pancreas = liver
Oskarsson and Tjalve, 1980	Mouse, 4	7 ug/kg (1.8 uCi ^{63}Ni/animal One iv dose[d]	Kidney > serum > lung > liver > erythrocytes > brain
Bergman et al., 1980	Mouse, 3	10 ug/animal. (100 uCi ^{63}Ni). One iv dose[e]	Kidney > lung > skin, hair follickle = blood = cartilage = eye retina > oral epithelium = teeth, enamel = teeth, dentine = salivary glands = liver > gastric mucosa = pancreas = spleen = brown fat > muscle > bone > central nervous system

Table 7 continued.

Authors	Animal, group size	Dose[a]	Relative Distribution of ^{63}Ni
English et al., 1981	Rat, 4	100 nmoles (15 uCi ^{63}Ni/ animal) One intratracheal instillation	lungs > mediastinal lymph nodes > kedneys > heart > bone > ovaries > spleen = duodenum = skin = adrenals > liver = pancreas = pituitary
Sarkar, 1981	Rat	one i.p. injection[g]	Kidneys > lung > spleen = heart > liver > muscle

a Unless otherwise noted, animals were killed 2 h after the last injection of $^{63}NiCl_2$.
b Animals were killed 24 h after the last injection of $^{63}NiCl_2$.
c Groups of animals were killed 1 and 24 h postinjection.
d Animals were killed 4 h postinjection.
e Groups of animals were killed 1/2, 1, 2, 4, 8, 16 and 24 h postinjection.
f Groups of animals were killed 2, 4, 8, 12 and 24 h postinjection.
g Animals were killed 24 h after injection.

Table 8. Distribution of ^{63}Ni in tissues of rodents

Ref.	Animal group size	Dose	Days between dosage and killing	Relative distribution of ^{63}Ni
Herlant-Peers et al., 1982	Mouse, 4	11 ug Ni (50 uCi ^{63}Ni/animal). One ip dose	6	Lung > kidneys > skin > intestine > spleen > liver > uterus > stomach > brain > heart > muscle
Oskarsson and Tjalve, 1979a	Mouse, 3	4.6 ug Ni/kg (1.2 uCi ^{63}Ni/animal) One iv dose	5	Lung = kidney > sternal cartilage > liver > pancreas
			10	Lung > kidney > pancreas = sternal cartilage > liver
Bergman et al., 1980	Mouse, 3	10 ug/animal (100 uCi ^{63}Ni) One iv dose	2	Lung > skin > kidney > cartilage > muscle = liver = bone
			21	Lung > skin > kidney > cartilage > bone > liver > muscle
English et al., 1981	Rats, 4	100 nmoles (15 uCi ^{63}Ni/animal). One intratracheal instillation	7	Lungs > mediastinal lymph nodes > kidneys > pituitary = adrenals > liver = spleen = skin > bone > ovaries > duodenum > pancreas > heart
Carvalho and Ziemer, 1982	Rat, 5	1-27 ugNi (8 uCi ^{63}Ni/animal). One intratracheal instillation	3	Lungs > kidneys > bone = skin = spleen > liver testes

Table 9: Mutagenesis in microorganisms

Species	System	Compound	Concentration	Result	Author
T4 Bacteriophage		$NiSO_4$	300 ug/ml (67 ug Ni/ml)	-	Corbett et al., 1970
Bacillus subtilis	Rec.	$NiCl_2$	0.05 M (2.9 mg Ni/ml)	-	Nishioka, 1975
Bacillus subtilis	Rec.	$NiCl_2$	0.005-0.5 M (0.3-29 mg Ni/ml)	-	Kanematsu et al., 1980
		NiO	(0.3-29 mg Ni/ml)	-	
		Ni_2O_3	(0.6-59 mg Ni/ml)	-	
Eschericia coli	WP2 fluctuation test	$NiCl_2$	5-25 ug/ml (1.2-6.2 ug Ni/ml)	-	Green et al., 1976
Salmonella typhimurium	Reverse mutation TA 100	$NiCl_2$	10^{-6}M, 10^{-5}M, 10^{-4}M, 10^{-3}M, 10^{-2}M (0.06-587 ug Ni/ml)	-	Tso and Fung, 1981
Salmonella typhimurium	Reverse mutation TA 98, TA 100, TA 1535, TA 1537 TA 1538	$NICl_2$ and $NiSO_4$	Not stated	-	Arlauskas et al., 1985
Eschericia coli	WP 2 fluctuation test				
Corynebacterium sp. 887	Fluctuation test clone method	$NiCl_2$	0.031-10 ug/ml (0.08-2.5 ug Ni/ml)	+	Pikalek and Necasek, 1983
Eschericia coli (Repair-deficient strain)	Killing assay	$NiCl_2$	0-1000 ug/ml (0-247 ug Ni/ml)	+	Tweats et al., 1981
Saccharomyces cerevisiae	Reverse mutation in locus ilv 1, conversion in locus trp 5	$NiSO_4$	0.005-0.04 M (0.3-2.3 mg/ml)	- (+)	Singh, 1984

Table 10: Mutagenesis in mammalian cells

Cell type	System	Compound	Concentration	Result	Author
CHO cells (Chinese hamster ovary cells)	Induction of 6-thio-guanine resistant mutants (HGPRT-locus)	$NiCl_2$	Not stated	+	Hsie et al., 1984
V79 Chinese hamster cells	Induction of 8-aza-guanine resistant mutants (HGPRT-locus)	$NiCl_2$	0.4-0.8 mM (23-47 ug Ni/ml)	+	Miyaki et al., 1979
L51784 Y/TK $^{+/-}$ mouse lymphoma cells	Induction of trifluoro-thymidineresistant mutants (TK locus)	$NiCl_2$	2.25-7.12 x 10^{-4}M (13-42 ug Ni/ml)	+ (dose-dependent number of Mutations)	Amacher and Paillet, 1980

Table 11: DNA lesions and induction of DNA-repair mechanism

Cell type	System	Compound	Concentration	Result	Author
Sprague-Dawley rat i.p. adm. Tissues from kidney, liver, lung and thymus analysed	Alkaline elution	$NiCO_3$	5-40 mg/kg (2.5-20 mg Ni/kg)	Single strand Breaks in lung and kidney nuclei besides DNA-protein and DNA inter-strand cross-links in kidney nuclei.	Ciccarelli et al., 1981 Ciccarelli and Wetterhahn, 1982
CHO cells	Alkaline sucrose gradient sedimentation	$NiCl_2$	1 ug/ml and 100-500 uM (0.2 and 5.9-29 ug Ni/ml)	Single strand breaks	Robison and Costa, 1982
		Cryst. Ni_3S_2	10 ug/ml (7.3 ug Ni/ml)	Single strand breaks	Robison et al., 1982
		Cryst. NiS	1-10 ug/ml (0.6-6.5 ug Ni/ml)	Single strand breaks	
		Amorphous NiS	10 ug/ml (6.5 ug Ni/ml)	No single strand breaks	
CHO and SHE cells	Cesium chloride equilibrium gradient sedimentation of DNA or nucleoids	$NiCl_2$	100-1000 uM (5.9-59 ug Ni/ml)	Induction of DNA-repair	Robison et al., 1983, 1984.
		Cryst Ni_3S_2	10 ug/ml (7.3 ug Ni/ml)	do	
		Cryst. NiS	1-10 ug/ml (0.6-6.5 ug Ni/ml	do	
		Amorphous Nis	5-10 ug/ml (3.3-6.5 ug Ni/ml)	No significant induction of DNA-repair	
Human fibroblasts	Alkaline elution tion (with and without polymerase inhibitor)	$NiSO_4$	0.01-2 mg/ml (2.23-447 ug Ni/ml)	No single strand breaks	Fornace, 1982

Table 12: Chromosomal damage in vivo

Species	System	Compound	Concentration	Route		Result	Author
Human	Lymphocytes	Mainly NiO and Ni_3S_2	0.1-0.5 mg Ni/m^3 air, mean 0.2 mg Ni/m^3 air	Occupa-tional exposure	(3-33 years)	+	Waksvik and Boysen, 1982
			0.1-1.0 mg Ni/m^3 air, mean 0.5 mg Ni/m^3 air		(8-31 years)		
Human	Lymphocytes	Mainly NiO and Ni_3S_2	More than 1 mg Ni/m^3 air	Occupa-tional exopsure	(25 years)	+	Waksvik et al, 1984
Rat	Bone marrow and sperma-togonial cells	$NiSO_4$	3-6 mg/kg (0.7-1.3 mg Ni/kg). 2 groups exposed.	i.p.		-	Mathur et al., 1978
Mouse	Dominant lethal test and micro-nucleus test	$Ni(NO_3)_2$	28 mg/kg (5.7 mg Ni/kg) 56 mg/kg (11 mg Ni/kg)	i.p.		-	Deknudt and Leonard, 1982
		$NiCl_2$	12.5 mg/kg (3.1 mg Ni/kg) 25 mg/kg (6.2 mg Ni/kg)	i.p.		-	
Mouse	Embryonic cells derived from treated male germ cells	$Ni(NO_3)_2$	56 mg/kg (11 mg Ni/kg)	i.p.		-	Jacquet and Mayence, 1982

Table 13: Chromosomal damage in vitro

Cell type	Compound	Concentration	Result	Author
Mammary carcinoma cells	$NiCl_2$	$2x10^{-4}$-$1x10^{-3}$M (12-59 ug Ni/ml)	No definite effect	Umeda and Nishimura, 1979
FM3A cells	$Ni(CH_3COO)_2$	$2x10^{-4}$-$1x10^{-3}$M (12-59 ug Ni/ml)	No definite effect	
	$K_2Ni(CN)_4$	$2x10^{-4}$-$1x10^{-3}$M (12-59 ug Ni/ml)	Gaps	
	NiS	$3.2x10^{-4}$-$2x10^{-3}$ (19-117 ug Ni/ml)	Gaps and breaks	
Mammary carcinoma cells	$NiCl_2$	$6x10^{-4}$-10^{-3}M (35-59 ug Ni/ml)	Gaps, breaks and fragmentations for all substanses	Nishimura and Umeda, 1979
FM3A cells	$Ni(CH_3COO)_2$	$6x10^{-4}$-10^{-3}M (35-59 ug Ni/ml)		
	$K_2Ni(CN)_4$	1-$1.6x10^{-3}$M (59-94 ug Ni/ml)		
	NiS	4-$8x10^{-4}$M (23-47 ug Ni/ml)		
SHE cells and human lymphocytes	$NiSO_4$	$1.9x10^{-5}$M (1.1 ug Ni/ml)	Gaps and breaks	Larramendy et al., 1981
CHO cells	$NiCl_2$	1-1000 uM (0.06-59 mg Ni/ml)	Gaps, breaks and exchanges	Sen and Costa, 1985
	Cryst NiS	5-20 ug/ml (3.2-13 ug Ni/ml)		

Table 14: Sister Chromatid exchange. In Vivo and in Vitro

Cell type	Compound	Concentration	Result	Author
Human lymphocytes occupational exposure (3-33 years)	Mainly NiO and Ni_3S_2	Less than 1 ug Ni/m^3	No increased rate	Waksvik and Boysen, 1982
Human lymphocytes occupational exposure (more than 25 years)	Mainly NiO and Ni_3S_2	More than 1 ug Ni/m^3	No increased rate	Waksvik et al., 1984
FM3A cells (mammary carcinoma cells)	$NiCl_2$	$6x10^{-4}$-10^{-3}M (35-59 ug Ni/ml)	Increased rate after a recovery period	Nishimura and Umeda, 1979
	$Ni(CH_3COO)_2$	$6x10^{-4}$-10^{-3}M (35-59 ug Ni/ml)		
	$NiK_2(CN)_4$	1-$1.6x10^{-3}$M (59-94 ug Ni/ml)		
	NiS	4-$8x10^{-4}$M (23-47 ug Ni/ml)		
Human lymphocytes	$NiSO_4$	$2.33x10^{-6}$-$2.33x10^{-3}$M (0.1-137 ug Ni/ml)	Increased rate at conc. up to $2.33x10^{-4}$M (14 ug Ni/ml)	Wulf, 1980
SHE cells and human lymphocytes	$NiSO_4$	1-5 ug/ml (0.2-1.1 ug Ni/ml) 2.5-5 ug/ml (0.6-1.1 ug Ni/ml)	Increased rate	Larramendy et al., 1981

Table 14 continued.

Cell type	Compound	Concentration	Result	Author
Human lymphocytes	Ni_3S_2	0.001-100 ug/ml (0.0007-73 ug Ni/ml)	Increased rate at conc. 1-100 ug/ml (0.7-73 ug Ni/ml)	Saxholm et al., 1981
Don-cells (Chinese hamster cells)	$NiSO_4$	50 ug/ml (11 ug Ni/ml)	Increased rate	Ohno et al., 1982
	$NiCl_2$	32 ug/ml (7.9 ug Ni/ml)		
Human lymphocytes	$NiCl_2$	10^{-6}-10^{-3}M (0.06-59 ug Ni/ml)	Increased rate at conc. $1.19x10^{-4}$M to $5x10^{-4}$M (7.0-29 ug Ni/ml)	Newman et al., 1982
Human lymphocytes and P388D, cells	$NiSO_4$	10^{-4}M (5.9 ug Ni/ml)	Slightly increased rate	Andersen, 1983
CHO cells	Crystalline NiS	5-20 ug/ml (3.2-13 ug Ni/ml)	Increased rate	Sen and Costa, 1985
	$NiCl_2$	1-1000 uM (0.06-59 ug Ni/ml)		

Table 15: Cellular transformation of Mammalian Cells

Cell type	Compound	Concentration	Effect	Author
C3H/10T 1/2 cells	Ni_3S_2	0.001-0.1 ug/ml ($7.3x10^{-4}$-$7.3x10^{-2}$ ug Ni/ml)	Transformation to type I, II and III foci	Saxholm et al., 1981
BHK-21 cells (baby hamster kidney cells)	alpha-Ni_3S_2	5-20 ug/ml (3,7-15 ug Ni/ml)	Anchorage independency for all substances	Hansen and Stern, 1983
	Ni_2O_3	5-20 ug/ml (3.2-14 ug Ni/ml)		
	NiO	37.5-150 ug/ml (29-118 ug Ni/ml)		
	$Ni(CH_3COO)_2$	100-400 ug/ml (24-94 ug Ni/ml)		
	MIG welding fume from welding with a pure nickel wire	100-400 ug/ml		
Human bronchial epithelial cells	$NiSO_4$	5-20 ug/ml (1.1-4.5 ug Ni/ml)	Changes in growth control and morphology	Lechner et al., 1984
SHE cells	$NiSO_4$	2.5-10 ug/ml (0.6-2.2 ug Ni/ml)	Loss of contact inhibition	Di Paolo and Casto, 1979
	Ni_3S_2	1-5 ug/ml (0.7-3.7 ug Ni/ml)	do	
	amorphous NiS	5-20 ug/ml (3.2-13 ug Ni/ml)	No effect	
SHE cells	amorphous NiS	2 and 5 ug/ml (1.3 and 3.2 ug Ni/ml)	No effect	Costa et al., 1978
	alpha-Ni_3S_2	2 and 5 ug/ml (1.5 and 3.7 ug Ni/ml)	Loss of contact inhibition	

Table 15 continued.

Cell type	Compound	Concentration	Effect	Author
SHE cells	alpha-Ni_3S_2	0.1-1.0 ug/ml (0.07-0.7 ug Ni/ml)	Induction of sarcomas in nude mice by implantation	Costa et al., 1979
SHE cells	$NiSO_4$	100-200 ug/ml (22-45 ug Ni/ml)	Enhancement of viral transformation	Casto et al., 1979a
SHE cells for transformation studies and CHO cells for phagocytosis studies	Crystalline and amorphous NiS	0.1-10 ug/ml (0.06-6.5 ug Ni/ml)	No contact inhibition. Transformation activity related to cellular uptake by phagocytosis. Crystalline NiS with negative surface charge more potent than amorphous NiS	Costa and Heck, 1982 Abbracchio et al., 1982a Costa and Mollenhauer, 1980b Heck and Costa, 1982 Costa et al., 1981a Costa, 1979
	Ni_3S_2	0.1-10 ug/ml (0.07-7.3 ug Ni/ml)		
	$NiCl_2$	5-20 ug/ml (1.2-4.9 ug Ni/ml)		
	Ni_3Se_2	0.1-5 ug/ml (0.05-2.6 ug Ni/ml)		
SHE cells	$NiSO_4$	0.5-20 ug/ml (0.1-4.5 ug Ni/ml)	Synergistic effect with Benzo(a)pyrene, N-hydroxy-2-acetyl-aminofluorene, 4-nitroquinoline-1-oxide and cigarette smoke	Rivedal et al., 1980 Rivedal and Sanner, 1980, 1981, 1982

Table 16: Intramuscular injection

Species	No of animals	Compound	Dose	Tumor incidence	Author
Fisher rats	10 per group	alpha-Ni_3S_2	5 mg/rat (3.7 mg Ni/rat)	80%	Sunderman and Maenza, 1976
			20 mg/rat (15 mg Ni/rat)	100%	
		amorphous NiS	5.6 mg/rat (3.6 mg Ni/rat)	0%	
			22.4 mg/rat (14 mg Ni/rat)	0%	
		Ni-dust	3.6 mg/rat	0%	
			14.4 mg/rat	22%	
		Ni-Fe-S	9.2 mg/rat (5 mg Ni/rat)	10%	
			36.8 mg/rat (20 mg Ni/rat)	80%	
Syrian golden hamster	15	alpha-Ni_3S_2	5 mg/hamster (3.7 mg Ni/hamster)	33%	
	17		10 mg/hamster (7.5 mg Ni/hamster)	71%	
Fisher rats	20	metallic Ni-dust	14 mg Ni/rat	65%	
	23	crystalline Ni_3Se_2	do	92%	
	16	crystalline NiSe	do	50%	
	9	crystalline alpha-Ni_3S_2	do	100%	
	14	crystalline beta-NiS	do	100%	
	10	amorphous NiS	do	0%	
	29	alpha-Ni_3S_2	0.63 mg/rat	24%	
	9	alpha-Ni_3S_2	20 mg/rat	100%	

Table 16 continued.

Species	No of animals	Compound	Dose	Tumor incidence	Author
Hooded rats	20	Ni_3S_2	10 mg/rat (7.3 mg Ni/rat)	55%	Yamashiro et al., 1980
Fisher rats	63		do	94%	
Wistar rats	20 in each group	colloidal $Ni(OH)_2$	120 umol/rat (7 mg Ni/rat)	0%	Kasprzak et al., 1983
		airdried $Ni(OH)_2$	do	25%	
		crystallized $Ni(OH)_2$	do	15%	
		Ni_3S_2	40 umol/rat (2.3mg Ni/rat)	80%	
		$NiSO_4$	66 umol/rat (3.9 mg Ni/rat)	0%	
Fisher rats	20	NiAs	14 mg Ni/rat	0%	Sunderman and McCully, 1983b
	16	$Ni_{11}As_8$	do	50%	
	20	Ni_5As_2	do	85%	
	16	NiAsS	do	85%	
	29	NiSb	do	59%	
	26	NiTe	do	54%	
Pregnant Fisher rats	8	Ni_3S_2	20 mg/rat (15 mg Ni/rat)	Sarcomas in dams, no exess tumors in progeny	
Fisher rats		Ni_3S_2	2.5 mg/rat (1.8 mg Ni/rat)	98%	Sunderman et al., 1974
		Ni_3S_2 + Al (equimolar)	do	96%	
		Ni_3S_2 + Cu (do)	do	100%	
		Ni_3S_2 + Cr (do)	do	100%	
		Ni_3S_2 + Mn (do)	do	63%	

Table 16 continued.

Species	No of animals	Compound	Dose	Tumor incidence	Author
Fisher rats	20 per group	Ni_3S_2	10.4 umol/site (0.6 mg/site)	70%	Kasprzak et al., 1985
		Ni_3S_2+ 3% dietary $Ca(CH_3COO)_2$ (3 months)	do	90%	
		Ni_3S_2+ 3% dietary $Ca(CH_3COO)_2$ (6 months)	do	85%	
		Ni_3S_2+ 3% dietary $Mg(CH_3COO)$ (3 months)	do	75%	
		Ni_3S_2+ 3% dietary $Mg(CH_3COO)_2$ (6months)	do	85%	
		Ni_3S_2+ 0.16 mmol $Ca(CH_3COO)_2$ /kg inj. s.c. 3 x/week (1 month)	do	100%	
		Ni_3S_2+ 0.16 mmol $Ca(CH_3COO)_2$ /kg inj. s.c. 3 x/week (4 months)	do	100%	
		Ni_3S_2+2 mmol $Mg(CH_3COO)_2$ /kg inj. s.c. 3 x week (1 month)	do	100%	
		Ni_3S_2+ 2 mmol $Mg(CH_3COO)_2$ /kg inj. s.c. 3 x/week (4 months)	do	95%	
		Ni_3S_2 coinjected with 62 umol $CaCO_3$	do	85%	
		Ni_3S_2 coinjected with 62 umol $MgCO^3$	do	25%	

Table 16 continued.

Species	No of animals	Compound	Dose	Tumor incidence	Author
Fisher rats	30	alpha-Ni_3S_2	1.2 mg/rat (0.9 mg Ni/rat)	77%	Sunderman et al., 1976
	14	alpha-Ni_3S_2 + Mn-dust (lung)	do	7%	
	15	alpha-Ni_3S_2 + Cr-dust (lung)	do	80%	
Fisher rats	24	alpha-Ni_3S_2	2.5 mg/rat (0.611 mg Ni/rat)	96%	Sunderman and McCully, 1983a
	23	alpha-Ni_3S_2 + Mn-dust (2 mg Mn)	do (coinjected in one thigh)	61%	
	24	alpha-Ni_3S_2 + Mn-dust (2 mg Mn)	2.5 mg/rat (0.611 mg Ni/rat) injected in opposite thigh)	100%	
	27	alpha-Ni_3S_2	1.2 mg/rat (0.9 mg Ni/rat)	48%	
	19	alpha-Ni_3S_2 + MnS (1 mg Mn)	do	55%	
	20	alpha-Ni_3S_2 + Mn_2O_3 (1 mg Mn)	do	40%	
	20	alpha-Ni_3S_2 + MnO_2 (1 mg Mn)	do	40%	
	17	alpha-Ni_3S_2 + $Mn_2(CO)_{10}$ (1 mg Mn)	do	76%	

Table 17: Intrarenal injection

Species	No of animals	Compound	Dose	Tumor incidence	Author
Spraque-Dawley rats	16	alpha-Ni_3S_2	10 mg/kidney (7.4 mg Ni)	44%	Jasmin and Riopelle, 1976
	24	do	do	46%	
	20	do	do	55%	Jasmin and Solymoss, 1977
	20	Metallic Ni-dust	10 mg Ni/kidney	0%	
	18	NiS	10 mg/kidney (6.4 mg Ni)	0%	
Wistar-Lewis rats	11	alpha-Ni_3S_2	5 mg/rat (3.7 mg Ni/rat)	64%	Sunderman et al., 1979a
NIH Black rats	12	do	do	50%	
Long-Evans rats	12	do	do	0%	
Fisher rats	32	do	do	28%	
Fisher rats	38	do	10 mg/rat (7.3 mg Ni)	75%	
Fisher rats	28	alpha-Ni_3S_2 + Mn(6.9 mg/rat)	10 mg/rat (7.3 mg Ni)	32%	

Table 17 continued.

Species	No of animals	Compound	Dose	Tumor incidence	Author
Fisher 344 rats	18	Ni-dust	7 mg Ni/rat	0%	Sunderman, 1984
	12	NiO	do	0%	Sunderman and Hopfer, 1983
	10	NiS_2	do	20%	
	14	Beta-NiS (cryst.)	do	57%	
	15	NiS (amorphous)	do	0%	
	15	alpha Ni_3S_2	do	27%	
	12	NiSe	do	8%	
	23	Ni_3Se_2	do	8%	
	19	NiTe	do	0%	
	15	NiAsS	do	20%	
	20	NiAs	do	5%	
	15	$Ni_{11}As_8$	do	0%	
	17	Ni_5As_2	do	0%	
	20	NiSb	do	0%	
	12	Ni_4FeS_4	do	8%	
	14	$NiFe_{1.6}$ (allay)	do	7%	
	19	$NiTiO_3$	do	0%	

Table 18: Epidemiological studies of nickel-production workers.

Population	Exposure Period	Follow-up Period	Cohort Size	Comparison Population	Excess Cancer risk	Literature Reference	Section
Copper Cliff sinter plant	1948-1962	1963-78	495	Province	Lung, nasal	Chovil et al., 1981	3.5.2
Sudbury and Port Colborne Process staff	1902-1976	1950-76	54,724	Province	Lung, nasal	Roberts et al., 1984	3.5.2
Falconbridge mines, mills smelter	1929-1976	1950-76	11,594	Province	None	Shannon et al., 1984	3.5.3
Huntington refinery	1922-1947	1948-77	266	Internal, local and national	Nasal	Enterline and and Marsh, 1982	3.5.4
Falconbridge refinery	1910-1969	1953-79	2,247	National	Lung, nasal, laryngeal	Magnus et al., 1982	3.5.5
Clydach refinery	1902-1949	1934-81	945	Local and national	Lung, nasal	Peto et al., 1984	3.5.6
Fort Saskatchewan refinery	1954-1978	1954-78	720	Province	None	Egedahl and Rice, 1984	3.5.7

Table 19: Embryotoxicity and teratogenicity

Species	No. of animals	Period of gestation	Compound	Dose	Route	Effect	Author
Rat		Throughout gestation	$NiCO_3$	0.25-1 g Ni/ kg of food	peroral	Normal litter size and body weight. Increased Ni content of pubs at 0.5-1 g Ni/kg of food.	Phatak and Patwardhan, 1950
Chick		Day 4 and 8	$NiCl_2$	0.05-0.08 mg Ni/egg		LD_{50}=0.05 mg Ni/kg (when administered on day 4 of gestation).	Ridgway and Karnofsky, 1952
Rat	5 pairs	Lifespan of 3 generations	Ni ions	5 mg Ni/l in drinking water.	peroral	Increased runts and neonatal death in 3 generations. Changed sex ratio in 3rd generation.	Schroeder and Mitchener, 1971
Hamster		Day 8	$Ni(CH_3COO)_2$	(2-30 mg/kg (0.5-7 mg Ni/kg) body weight).	i.v.	Increased number of resorbed and death embryos.	Ferm, 1972

Table 19 continued.

Species	No. of animals	Period of gestation	Compound	Dose	Route	Effect	Author
Wistar rats	20 pairs 20 pairs 20 pairs	Life span of 3 generations.	$NiSO_4$	250 mg Ni/kg food 500 mg Ni/kg food 1000 mg Ni/kg food	peroral	Increased incidence of still born pups in first generation stall diatary levels and decreased body weights of weanlings in all generations at 1000 mg Ni/kg food.	Ambrose et al., 1976
Rat	7	Day 8	$NiCl_2$	16 mg Ni/kg	i.m.	Reduction of no. of live pups. Lower body weight of pups. 4, 6 and 8 weeks after delivery.	Sunderman et al., 1978b
	12	Day 8	$NiCl_2$	8 mg Ni/kg	i.m.	No effect	
	11	do		12 mg Ni/kg	do	Reduction of no. of live pups.	
	12	do		16 mg Ni/kg	do	Reduction of no. of live pups besides reduced body weights of fetus.	

Table 19 continued.

Species	No. of animals	Period of gestation	Compound	Dose	Route	Effect	Author
Rat	12	Day 6-10	$NiCl_2$	1.5-2 mg Ni/kg (2 times a day for 5 days).	i.m.	No effect	
	13	do			do	Reduction of no. of live pups.	
	10	Day 18	$NiCl_2$	6 mg Ni/kg	i.m.	No effect	
	12	do		8 mg Ni/kg	do	No effect	
	15	do		16 mg Ni/kg	do	Increase og fetal mortality obviously since greath toxicity to the dams.	
	12	Day 6	Ni_3S_2	80 mg Ni/kg	i.m.	Reduction in no. of live pups.	
Mouse	10 in each group	Day 7-11	$NiCl_2$	1.2 mg Ni/kg	i.p.	Increased resorption rates. Decreased fetal weight. Delay in skeletal ossification and a higher incidence of malformations.	Lu et al., 1979
		do		2.3 mg Ni/kg			
		do		3.5 mg Ni/kg			
		do		4.6 mg Ni/kg			
		do		5.7 mg Ni/kg			
		do		6.9 mg Ni/ injected one of 5 days.			
Chick	840 eggs	Day 0,1,2,3 or 4 of incubation	$NiCl_2$	0.02-0.7 mg/egg (5-173 ug Ni/egg	injected into air sac of egg	Reduced body size, hemorrhage and malformations.	Gilani and Marano, 1980

Table 19 continued.

Species	No. of animals	Period of gestation	Compound	Dose	Route	Effect	Author
Rat	10	Throughout gestation	NiO	0.8 mg (0.6 mg Ni)/m^3 1.6 mg (1.3 mg Ni)/m^3 3.2 mg (2.5 mg Ni)/m^3	inhalation	No effect. Reduced body weights of fetuses.	Weischer et al., 1980
Mouse		2 cell stage (day 2) 4-8 cell stage (day 3)	$NiCl_2$	10-1000 uM (0.6-59 mg Ni/litre)	in vitro	Growth inhibition at 0.6 mg Ni/l on day 2 and 18 mg Ni/l on day 3.	Storeng and Jonsen, 1980
Mouse	26-30 in each group	Day 1-6	$NiCl_2$	20 mg/kg (4.9 mg Ni/kg) injected one of 6 days	i.p.	Increased resorptions and deaths. Fetal anomalies and decreased body weight.	Storeng and Jonsen, 1981
Rats	8	Day 6	Ni_3S_2	20 mg (15 mg Ni)	i.m.	Reduced bodyweight of progeny at the age of 6, 12, 18 months. No malformations or exess tumors observed during the whole lifespan.	Sunderman et al., 1981

Table 19 continued.

Species	No. of animals	Period of gestation	Compound	Dose	Route	Effect	Author
Rat	7	7 days before gestation	Ni_3S_2	10 mg Ni/rat (30 mg Ni/kg)	intra-renal (i.r.)	Erythrocytosis in dams but not in the pups.	Sunderman et al., 1983
Mouse		4-8 cell-stage (day 3) Morula (day 4)	$NiCl_2$	400 uM (24 mg Ni/l) 5 min.- 48 hours	in vitro	Toxic effect on the embryo. Transfer to $NiCl_2$-free medium after 5 min., 1 h and 3 h exposure resulted in regaining of developmental capacity.	Storeng and Jonsen, 1984
Rat	4 dams in each group.	Day 8, 12 or 16.	$NiCl_2$	1.2 or 4 mg Ni/kg	i.p.	Malformations.	Mas et al., 1985

TABLE 20.

Occupational exposure limits for nickel (data from IRPTC).

	Nickel metal, sparingly soluble compounds	Soluble nickel compounds
Czechoslovakia	0.05	0.05
Denmark	0.5	1
Federal Republic of Germany	0.5[a]	0.05
United Kingdom	1	0.1
Japan	1	1
Netherlands	1	0.1
Norway	0.1	0.1
Soviet Union	0.5[b]	0.005[b]
Sweden	0.5[c]	0.1[d]
USA (ACGIH)	1	0.1
USA (OSHA)	1	1

a respirable, technical guideline only
b aerosols, ceiling value
c nickel metal only; for nickel subsulfide, 0.01
d nickel compounds

Table 21: Studies of the relation between air nickel levels and urinary or plasma/serum nickel levels used in figures 2-5.

A	INCO Refinery, Clydach, Wales (Morgan and Rouge, 1984).
B	Falconbridge Refinery, Kristiansand, Norway (Hogetveit et al., 1978).
C	Welding (Zober et al., 1984b).
D	Electrolytic nickel refinery workers (Raithel et al., 1985).
E	Production of soluble nickel salts (Morgan and Rouge, 1979).
F	Nickel Alloy workers (Raithel et al., 1985).
G	Electrolytic nickel refinery workers (Bernacki et al., 1978a).
H	Flame cutters (Aitio et al., 1985).
I	Air craft engine production (Bernacki et al., 1978a).

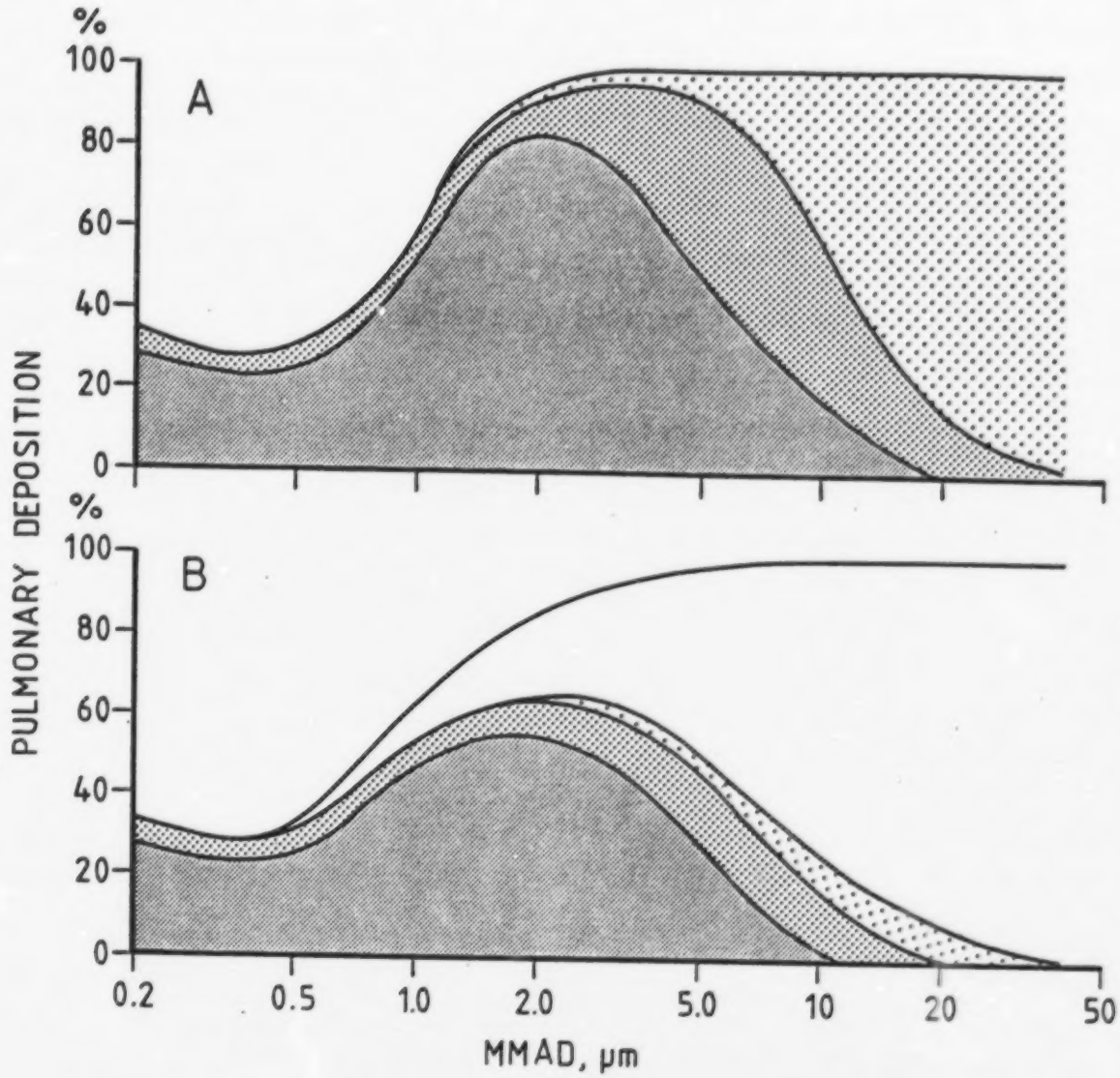

Fig. 1: Deposition of particles in the airways. Modified from: Lidwell, 1970. The curves were produced by employing calculations of Findeisen (1935) on results of Landahl and Tracewell (1949) assuming a ventilation rate of 15 per minute and a maximal air flow of 18 L/min.

A. Breathing through the mouth

B. Breathing througt the nose

- Alveoli
- Bronchioli
- Trachea + Bronchii
- Nose

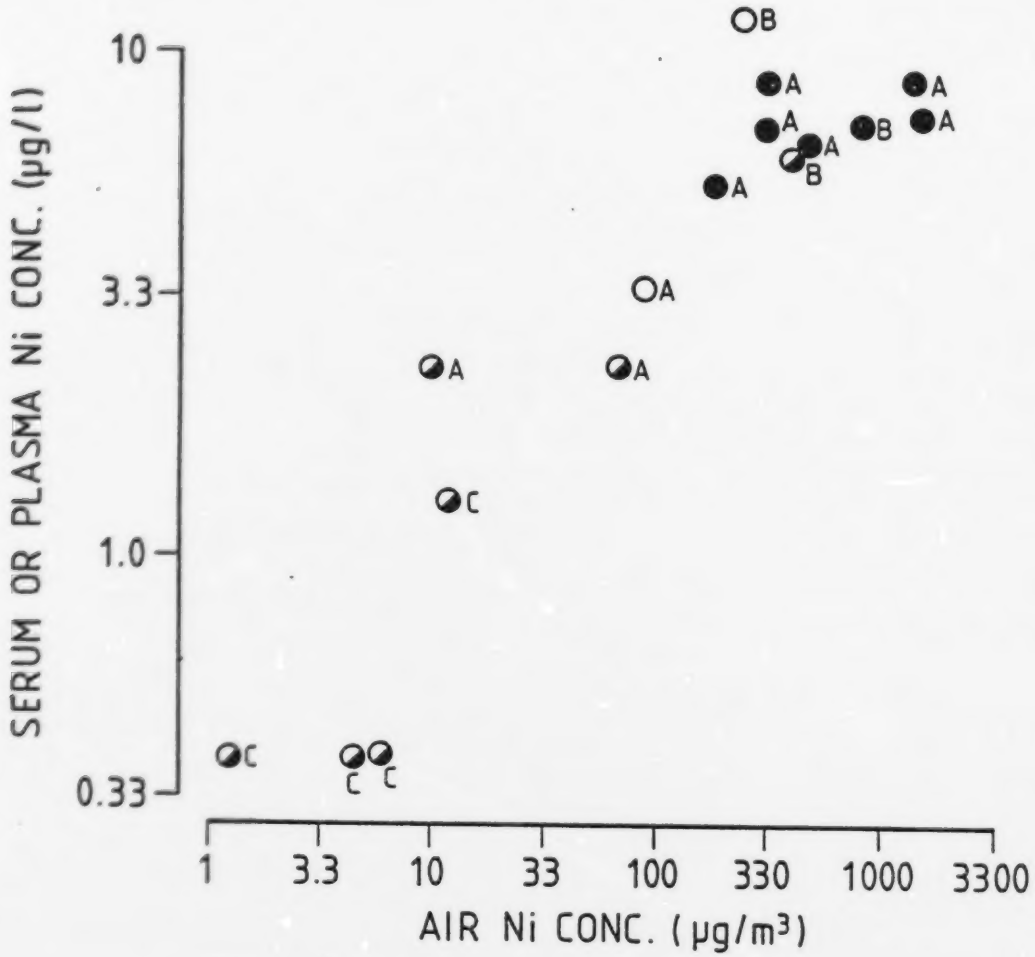

Fig. 2: Relationship between air nickel levels and serum or plasma nickel levels during various occupational exposures. The sources are identified in table 21.

● Exposure to insoluble nickel compounds
◐ Mixed exposures
○ Exposure to soluble nickel compounds

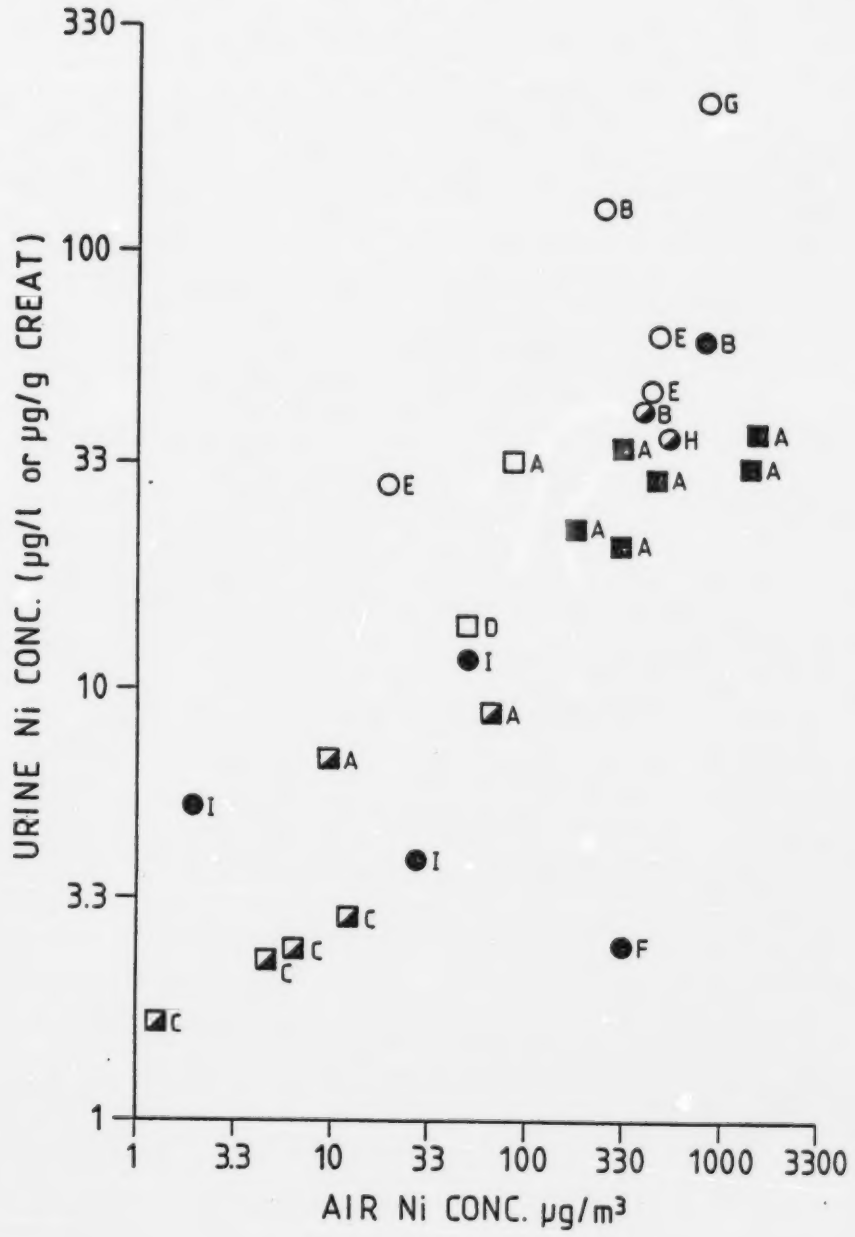

Fig. 3: Relationship between air nickel levels and urinary nickel levels during various occupational exposures. The sources are indicated in tabel 21.

Circles: ug Ni/L of urine
Squares: ug Ni/G of creatinine

■ Insoluble nickel compounds
◪ Mixed exposures
□ Soluble nickel compounds

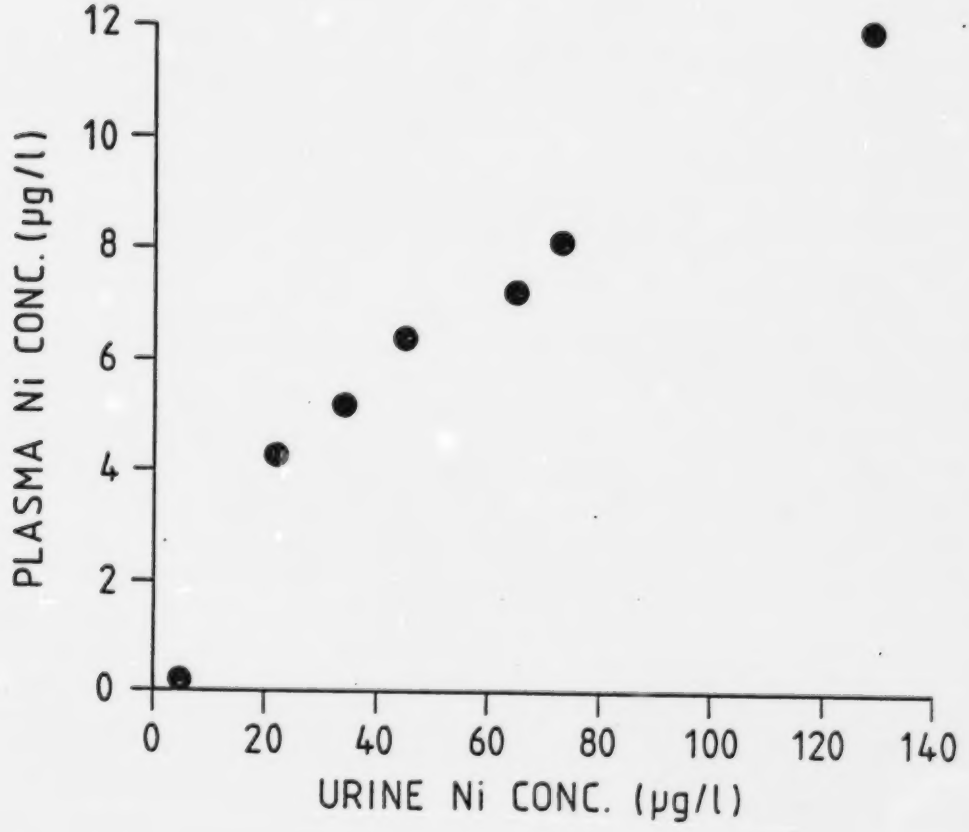

Fig. 4: Relationship between urinary and plasma nickel concentrations among different groups of workers at the Falconbridge refinery in Kristiansand, Norway. Data from Hogetveit et al. (1978) and Torjussen and Andersen (1979).

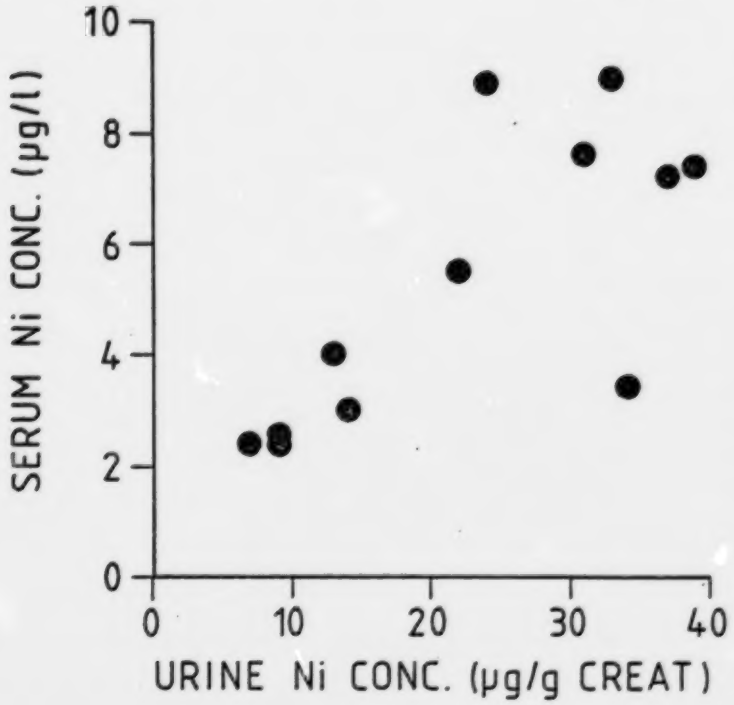

Fig. 5: Relationship between urinary and serum nickel concentrations among different groups of workers at the INCO nickel refinery in Clydach, Wales. Data from Morgan and Rouge (1984).